MULTIPLE CHEMICAL SENSITIVITIES AND THEIR RELEVANCE TO PSYCHIATRIC DISORDERS

Workshop Proceedings

Ottawa, Ontario
December 7, 1992

Health Canada Santé Canada

Canada

Proceedings of a Workshop

MULTIPLE CHEMICAL SENSITIVITIES AND THEIR RELEVANCE TO PSYCHIATRIC DISORDERS

Ottawa, Ontario
December 7, 1992

Organized by
Mental Health Division, Health Services Directorate
Health Programs and Services Branch
&
Laboratory Centre for Disease Control
Health Protection Branch

Health Canada
(formerly Health and Welfare Canada)

Editor: Dr. Tom Wood

ACKNOWLEDGEMENTS

This workshop and publication were made possible through financial support from Health Canada: the Mental Health Division, Health Services Directorate and the Program Promotion Division, Health Promotion Directorate, Health Programs and Services Branch and the Laboratory Centre for Disease Control, Health Protection Branch.

The organizers wish to express particular gratitude not only to the chairperson and presenters, but also to the rapporteurs, members and observers of the working groups, and all participants of the workshop.

Special thanks to the following for their assistance in organizing this workshop and the publication of the proceedings:

Ms. Anna Maria Alessi
Ms. Michèle Bélanger
Dr. John Davies
Ms. Barbara Dubuc
Ms. Gweneth Gowanlock
Dr. Barry Jones
Dr. Felix Li
Ms. Louise McRae
Ms. Judith Shane
Ms. Kathryn Wilkins

The views expressed within this document are those of the speakers and participants of the workshop and do not necessarily represent the views of Health Canada.

Additional copies are available from: Bureau of Chronic Disease Epidemiology, Laboratory Centre for Disease Control, Health Canada, Tunney's Pasture, Ottawa, Ontario, K1A 0L2.
Tel: (613) 941-8630 Fax: (613) 941-2057.

Version française de cette publication disponible sur demande.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

PREFACE

PRESENTATIONS

1. CHEMICAL SENSITIVITIES - THE CLINICAL PICTURE:
   by Roy Fox, BSc, MD, FRCPC, FRCP, FACP

2. CASE COMPARISON STUDY OF CHEMICALLY SENSITIVE PATIENTS:
   by Nancy Fiedler, PhD

3. DEPRESSION, SOMATIZATION, AND CHRONIC FATIGUE:
   by Susan Abbey, MD, FRCPC

4. PROVOCATIVE CHALLENGE IN PATIENTS WITH MULIPLE CHEMICAL SENSITIVITIES:
   by Arthur Leznoff, MD, FRCPC

5. OBSERVATIONS AND FEATURES OF CHEMICAL SENSITIVITY:
   by Nicholas Ashford, PhD, JD

6. ADAPTATION AND CONTROLLED CHALLENGES:
   by Claudia Miller, MD, MS

7. DISCRIMINATING BETWEEN CHEMICAL SENSITIVITIES AND AFFECTIVE DISORDERS:
   by Iris Bell, MD, PhD

8. BIOLOGICAL MARKERS IN MULTIPLE CHEMICAL SENSITIVITY:
   by Eric Nisbet-Brown, MD, PhD

9. THE ENVIRONMENTAL CONTROL UNIT IN DIAGNOSIS:
   by Gerald Ross, MD, CCFP, DIBEM, FAAEM

REPORTS FROM THE WORKING GROUPS

1. DIAGNOSTIC STATEMENT
   Chairperson and Rapporteur: Lynn Marshall, MD, FAAEM,

2. RESEARCH STATEMENT
   Chairperson and Rapporteur: Eric Nisbet-Brown, MD, PhD

APPENDICES:

A. LIST OF SPEAKERS

B. LIST OF PARTICIPANTS

PREFACE

There are people who are unusually sensitive to chemical and other substances in the environment and a diagnostic label of Multiple Chemical Sensitivities (MCS) is being applied frequently. There are no reliable data on the prevalence of MCS. In fact, there are no reliable diagnostic criteria yet established. Symptoms may be related to many organ systems, but central neurologic and mucosal symptoms frequently stand out. The non-specific nature of the complaints, lack of abnormal objective findings, and absence of a generally accepted diagnostic laboratory test make diagnosis of MCS difficult.

The chronic nature of the complaints in MCS patients associated with symptoms of central nervous system dysfunction such as depression, anxiety, irritability and difficulty concentrating may lead to psychiatric diagnosis such as major depression, neurasthenia or somatization disorder. Psychiatric diagnoses are descriptive labels for a set of signs and symptoms and do not offer an etiological explanation for them. "Symptomatology related to multiple chemicals is a distinct feature of these patients that is not classifiable by existing criteria used in conventional medical practice for psychiatric or physical illness and cannot be uniquely coded in either DSM III-R* or ICD-9**" ("Multiple Chemical Sensitivities", National Research Council, Washington, 1991). On the other hand, patients with MCS may show improvement with antidepressant and cognitive therapy. An overlap between the biology of depression and certain MCS and multiple food sensitivities syndromes has been suggested.

"The emergence of multiple chemical sensitivity as a phenomenon that needs investigation coincides with recognition that myriad exposures to environmental agents are sustained in indoor and outdoor environments" (National Research Council, Washington, 1991). The challenge is for the clinical investigator to determine whether adverse health effects are associated with low level exposures to these chemicals.

In May 1990, the Laboratory Centre for Disease Control (LCDC) held a workshop to identify and develop priorities for multidisciplinary research and to identify education/health promotion needs and explore social problems of affected persons. The workshop proceedings were published in Chronic Diseases in Canada (1991).

To further explore the issue of MCS, and particularly its relevance to psychiatric disorders, the workshop on "Multiple Chemical Sensitivities and Their Relevance to Psychiatric Disorders" was organized by the Mental Health Division, Health Programs and Services Branch, and the Laboratory Centre for Disease Control, Health Protection Branch.

The workshop consisted of presentations by experts in the relevant areas followed by two working group sessions focused on specific tasks. The following proceedings contain a summary of the presentation by each of the speakers and a report from each of the working groups. The speakers' original papers on which their presentations were based are included in the appendix.

* Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised, American Psychiatric Association, Washington, DC, 1987.

** International Classification of Diseases - 9th Revision. World Health Organization, 1977.

PRESENTATIONS

1. CHEMICAL SENSITIVITIES - THE CLINICAL PICTURE: Roy Fox, BSc, MD, FRCPC, FRCP, FACP

Symptoms of chemical sensitivity (CS) began to appear at Camp Hill Hospital, a general hospital and former veterans' hospital in Halifax, Nova Scotia, soon after the Veterans Memorial Building was opened in 1987. Six hundred individuals have now been affected and at least a hundred appear to have CS. Dr. Gerald Ross, who will speak later, has examined 32 of them in detail, all of whom have had chemical sensitivity confirmed.

Twenty-nine of these individuals were female, and three were male. Their ages ranged from 24 to 56, with a mean of 35. Thirteen were nurses, five were secretaries or clerks, three were occupational therapists, and three were nursing assistants. One physiotherapist, one psychologist, one social worker, one physician, one telephone operator, and one kitchen worker made up the rest of the group.

Ninety-four percent of the people suffered headaches, and 78% had confusion; 50% reported getting lost in their car or when walking, and losing things. One hundred percent had impaired memory, difficulty in concentrating, and irritability; 91% reported mood swings, and 75% had depression. Some people experienced tingling of their extremities constantly, but most people said it was part of their reaction to an environmental excitant, and they experienced paraesthesia in the hands, legs, and feet. In two individuals, there was objective evidence of neuropathy. Many people complained of dizziness when they entered the Veterans Building and 56% had a positive Romberg test on examination. The incidence of mental problems was higher in the patients with the neurological complaints.

One hundred percent felt fatigued, 81% had arthralgias, and 87.5% had myalgias as well. Several people have been diagnosed as having seronegative rheumatoid arthritis.

About half of the individuals examined complained of swelling of the legs and/or face, 22% had petechiae, and 53% said they bruised easily.

Increased sensitivity to cold occurred in 56%, cold extremities in 59% and Raynaud's phenomenon in 28% and these complaints appeared both in the chronic state and also when there was an acute reaction to the environment. The awareness of the cold extremities was often the first sign of a reaction. In one quarter of the individuals, symptoms progressed to the full picture of Raynaud's if they remained exposed. Skin problems were common, with adult-onset acne, dryness, itching, and dark circles under the eyes.

Seventy-two percent of the individuals complained of nausea, and constipation and/or diarrhea occurred in three quarters. Some had bloating and abdominal cramps.

Asthma was diagnosed in 20%, and respiratory problems were diagnosed in half of the 32. About three quarters had rhinorrhea or post-nasal drip.

More than a quarter had frequency or painful micturition and nocturia. Twenty-two percent of the people had urinary incontinence for the first time in this illness. As their health improved, these symptoms disappeared. Loss of libido occurred in all patients, and changes in menstrual flow was a common complaint.

A number of diagnoses in addition to CS were made on the 32 individuals investigated in detail. Twenty-two were found to have food sensitivity and 18 had toxic brain syndrome. Eight had reactive depression, six had asthma, five had hypertension, and three had fibromyalgia rheumatica. Two each had peripheral neuropathy, chronic fatigue syndrome, and urticaria.

Question from a member of the audience: *How many long-term residents of the Veterans' Building at Camp Hill Hospital developed symptoms?*

Dr. Roy Fox: *I proposed early on this should be looked at, but it wasn't. They have now been screened for skin rashes, and a few have been found, but no other significant problems.*

Comment from Dr. Iris Bell: You've made a major point here, that psychiatric disorders can co-exist. The presence of psychiatric problems can never rule out the presence of other disorders.

Dr. Susan Abbey: I know that you have a great interest in the concept of affective spectrum disorders which postulates that fibromyalgia, irritable bowel syndrome, CFS, etc. share some characteristics of affective disorders. My concern is also with patients who have had their primary psychiatric disorder misdiagnosed or undiagnosed. Certainly there are patients from both groups who can be effectively treated in 6 to 8 weeks with an antidepressant medication and do not need complex environmental medicine interventions.

Dr. Iris Bell: For some of the milder cases. In my clinical experience I've had a terrible time with these people because they don't tolerate the medications.

4. PROVOCATIVE CHALLENGE IN PATIENTS WITH MULTIPLE CHEMICAL SENSITIVITIES: Arthur Leznoff, MD, FRCPC

Multiple Chemical Sensitivities (MCS) symptoms are similar to those described in patients with multiple atypical food sensitivities, which I studied with Sharon Parker and other colleagues. In this study these patients could not distinguish their putative "allergenic food" from placebo. I had hoped to test MCS patients in a similar double-blind placebo-controlled study, but this could not be done because the patients said they were sensitive to all chemicals which would not allow a control. As well, some of the chemicals, such as cigarette smoke and formaldehyde, were impossible to disguise.

We identified 35 patients with the Cullen criteria (see page 18-19), and on interviews two patterns of symptomatology emerged. Twenty-five patients (referred to a Group A) reported that exposure produced breathlessness with no wheezing, and lightheadedness without vertigo. Some also developed headache, malaise, lightheadedness, impaired mentation, depersonalization, incoordination, breathlessness, paraesthesias, sweating and palpitations.

Ten patients (called Group B) reported tightness in the throat on exposure, a sensation of swelling in the throat, a sense of glands in the neck, choking, hoarseness, cough, loss of voice, and dysphonia.

Physical examination in both groups was normal. Patients in both groups complained of impaired mentation and fatigue.

Of the 25 patients with type A symptoms, 15 agreed to challenge tests, and they were exposed to aerosols such as Javex, hair spray, and cigarette smoke. Before and after challenge they had Flow-Volume measurements, and measurements of carbon dioxide and oxygen in their arterial blood or end-tidal expiratory air were made. The few who did not allow arterial punctures had venous blood samples.

Of the 15 Group A people, 10 had breathlessness, lightheadedness, and incoordination on challenge. Blood gas studies prior to the study couldn't be obtained on two, but the carbon dioxide tensions (pCO_2) on 7 after exposure were extremely low (19, 20, 13, 22, 32, 29, and 20 mm Hg). Three patients with venous sampling also showed reduction in carbon dioxide. When these people started the experiment they were not hyperventilating, but soon after the challenge started they began.

The remaining 5 Type A patients developed no symptoms. Although they were challenged with greater concentrations than they were exposed to at home, these people did not hyperventilate.

Five of a total of 10 Type B subjects who allowed challenge had a fiberoptic laryngoscope inserted without local anesthetic and their vocal cords were observed before and after. Before and after phonography was also done. Four out of 5 of them developed no swelling or edema after exposure to the stimuli, and the before and after phonograms

were the same. The fifth had small excrescences on her vocal cords (polyps); when they were removed, her "chemical sensitivity" disappeared.

In the 10 cases with observed hyperventilation, the perception of the trigger resulted in an acute panic reaction. The dramatic hyperventilation and the fall in pCO_2 would produce Group A symptoms in anyone. There was also evidence of sympathetic and adrenergic stimulation, with pallor, sweating, tremulousness, and a rising cardiac rate. Electrolytes were measured on two patients and both showed a rapid fall in potassium, which occurs when there is a rapid release of nor-adrenalin. Removal of the trigger resulted in improvement.

In the other patients where the challenge didn't produce symptoms, a different mechanism must be involved. The Type B patients were experiencing globus hystericus.

MCS is an emotional disorder in the family of phobias and panic attacks.

Comment from Dr. Gerald Ross: If you attribute the response and the hyperventilation to a panic disorder, why is it not equally logical to assume that they are actually physiologically responding to that substance, with that particular cluster of symptoms?

Comment from Dr. Iris Bell: As a biological psychiatrist I have to point out there is a large literature suggesting there is an increased sensitivity to carbon dioxide in people with panic disorder tested under controlled conditions when people are not aware they were being exposed.

5. OBSERVATIONS AND FEATURES OF CHEMICAL SENSITIVITY*: Nicholas Ashford, PhD, JD

Chemically sensitive patients fall into four groups. (Table 1**) First, there are industrial workers who report symptoms of the same kind that patients who identify themselves as "chemically sensitive". They are primarily male, blue collar workers, 20 to 65 years old. These patients hardly ever see clinical ecologists or allergists; they generally go to occupational physicians or their own family practitioners. They may experience a sensitive reaction and stop working. Thus looking at a group of workers to determine the prevalence of Chemical Sensitivity (CS) does not take into account the self-selection out of the workforce or out of a particular workplace the group may have experienced.

People who occupy tight buildings make up a second group, and they are exposed to indoor air contaminants, tobacco smoke, carpeting and drugs. They are female more than male, or children who go to school in newly constructed or renovated buildings.

People in the third group live in contaminated communities, near toxic waste sites, or are exposed to aerial pesticides or ground water contamination. They are people of all ages, including infants and pregnant women, and the whole population may be involved here.

The people in the last group have a heterogeneous exposure history and are largely white, female middle-class to professional individuals, although some may live on farms.

From a scientific point of view, events in workplaces, tight buildings and communities offer a much better opportunity to examine CS than a physician's office. One can examine an entire exposed population and watch the problem evolve, and not wait until the patients are so sick that their own psychological problems confuse the etiology. New populations are constantly becoming available for study, such as veterans returning from the Gulf War who were exposed to petrochemical fumes and pesticides, among other substances.

The word sensitivity causes confusion. There are three types of sensitivity. (Figure 1**) First, there is Classical Sensitivity, as to lead, which occurs with exposures in parts per million or above. If a population of exposed individuals is examined when they first exhibit harmful effects, some people

exhibit symptoms at low exposure levels and others at high. In the workplace the workers might be called "sensitive", "normal", and "super" workers. Employers want to hire the "super" workers; the "sensitive" workers tend to quit.

This classical sensitivity must be distinguished from a second kind, atopy or allergy, where there is a group of people (such as hay fever sufferers) who have classical IgE sensitivity. Some of them may also have CS but many do not. Whether they have a genetic history or a psychological predisposition remains to be seen, but this is an "allergic" population which must not be confused with people with CS.

CS is a third and distinct type of sensitivity and is caused by some initiating event, possibly an exposure to a neurotoxic substance. In a rough survey of 6,000 people who indicated that they were affected by CS, 80% knew when their problems began. Of these, 60% said their problems began with exposure to a pesticide. Other sensitizing events were exposure to anaesthesia, pharmaceuticals (including psychotropic drugs), carpets, and more recently possibly petrochemicals in the Gulf War. There do not seem to be a lot of sensitizers; many more substances cause a reaction after the sensitization has occurred. There must be careful separation of substances which cause "sensitization" and substances which "trigger" a reaction after the sensitizing event. "Triggering" may be caused by many chemicals other than the sensitizing agent, and at lower levels of exposure than those involved in induction of the illness. The reaction seems to occur at part per billion exposure levels, and this suggests that amplification of sensitivity is a real event.

If cumulative exposure curves are calculated (Figure 2**), 100% of people will eventually be toxic to lead, while not everyone becomes allergic, and not everyone will develop CS.

Chemical sensitivity may begin with one sensitivity and spread to many other substances, including foods.

* Work done in conjunction with Dr. Claudia Miller
** Refer to figures and table in appendix C ("Chemical Sensitivity and Low-Level Exposures: Scientific and Policy Considerations" pp. 91)

6. ADAPTATION AND CONTROLLED CHALLENGES*: Claudia Miller, MD, MS

There may be a wide spectrum of sensitivities and mechanisms involved in chemical sensitivity. Many kinds of exposures produce stimulatory symptoms (such as feeling a little "hyper" while painting in a closed room), and with cessation of exposure, withdrawal symptoms (tiredness, irritability, lethargy, fatigue) occur. An individual's response to a single exposure (eg. to a solvent or pesticide) can be graphically represented by a sine wave. In people who are very sensitive, the sine wave would have a greater amplitude, and in healthy individuals with no sensitivity to that substance, it would have almost no amplitude at all.

During a single day one can be exposed to many, relatively low level chemical stimuli at different times, and the sine waves representing the effects of each exposure may overlap. How an individual feels at any point in time will be the result of prior and on-going exposures, and it may be impossible to associate symptoms to a particular exposure.

A further difficulty is introduced by the fact that people adapt, that is, they develop tolerance to their exposures within a short period of time. When exposure to a solvent, caffeine or other substances cease, individuals who report being chemically sensitive often report experiencing withdrawal symptoms. It has been observed by these patients that when they are de-adapted (that is, removed from possible incitants for a sufficient period of time, generally four to seven days), they may experience robust responses upon re-exposure. Challenges performed for scientific or legal purposes may not be positive unless the individual is in a deadapted state first. If a person is not de-adapted prior to challenges, falsely negative or positive responses may occur. That is, an

individual may be responding to prior exposures when a placebo is administered or fail to respond to a challenge substance if it has not been avoided for a sufficient period prior to challenge testing.

Testing should be conducted in an environmental unit so that the number of stimuli producing overlapping effects (overlapping sine waves) will be reduced. Patients' medications should be discontinued, and steroids gradually withdrawn whenever feasible. Food-sensitive individuals may need to be fasted (if their condition permits) from four to seven days, in order to test them in a baseline, de-adapted condition. Following de-adaptation, single food or chemical challenges can be administered and effects of particular exposures observed in the absence of "background".

Multiple mechanisms have been proposed to explain chemical sensitivity: nervous system and/or immune system dysfunction, enzyme detoxification abnormalities, and psychogenic causes. There is a paucity of controlled studies regarding immune system effects of exposures and no clinical marker for immunological dysfunction appears to be consistently abnormal in these patients.

An intriguing neurological hypothesis for chemical sensitivity involves sensitization of the olfactory-limbic system, part of the so-called primitive "smell" brain. Cutting through (transection of) the olfactory bulbs is an animal model for depression. The olfactory bulbs provide much of the input to the amygdala, popularly termed "emotion central", and to the hippocampus, which is critical for laying down new memories and which is thought to be especially sensitive to many neurotoxins. These patients' difficulties with mood and memory might be explained by alterations in the function of this portion of the brain.

Chemicals might affect the limbic area in one of two ways. First it has been demonstrated that some chemicals, including some very large molecules, may be transported directly to this part of the brain via olfactory nerve cells leading from the upper nose to the olfactory bulbs of the brain. Another, more plausible way, is by "kindling", which is a kind of sensitization of the neurons in the limbic area. Kindling is well described in the seizure literature, and it involves exposure to a strong electrical stimulus or repeated electrical stimuli which produce seizures and which result in a lowering of the threshold for reactivity. Subsequently, very small electrical stimuli provoke a seizure. In chemical sensitivity, chemicals, rather than electrical stimuli, may kindle or sensitize olfactory limbic pathways and thus cause memory, concentration, and mood alterations, as well as autonomic nervous system effects. A number of animal studies have demonstrated that chemicals, including some pesticides and solvents, can cause limbic sensitization.

* Work done with Dr. Nicholas Ashford

Comment from a member of the audience: *I've found a chapter in a book, "Neurotoxicity of Industrial and Commercial Chemicals", by Anger and Johnson, published by CRC Press, Volume 1, 1985. It contains a compilation of just under 150 industrial solvents and it contains information about everything that this room has been talking about, including symptomatology.*

7. DISCRIMINATING BETWEEN CHEMICAL SENSITIVITIES AND AFFECTIVE DISORDERS:

Iris Bell, MD, PhD

There is debate in occupational medicine that Chemical Sensitivities (CS) may be an atypical post-traumatic stress disorder (PTSD), even though one cannot always find a history of either a chemical spill or a traumatic life event. One of the biological models for PTSD in people is Time-Dependent Sensitization (TDS), a progressive amplification of responses to an initially novel stimulus by the passage of time between the first and later stimuli, usually 1 to 14 days. Most of the studies have been done by psychopharmacologists on behaviour in animals; to find behaviour in a sensitized organism shows that the nervous system has been affected. In animals pharmacological and non-pharmacological stimuli cross-react.

The foreignness, novelty, or stressfulness of the agent is critical. An intermittent exposure is essential too, because a continuous exposure produces tolerance. In one study, low doses, rather than higher doses, bring out sensitization. Estradiol accelerates the acquisition of sensitization; testosterone lessens the tendency towards it. Numerous structurally unrelated substances can produce sensitization, and animals which develop a sensitivity are identical to those which do not.

I think that environmental chemicals and life stressors both affect similar systems in the brain and produce processes of sensitization which cross-react and cross-sensitize each other, and which can look identical. All of us may be looking at a similar outcome, and we cannot know whether it is due to life stress or CS.

Cacosmia is a symptom in the normal population which is an altered sense of smell, an illness caused by chemical odours that others do not find a problem. I found that in over half of a group of almost 500 college students and older adults had problems with at least one chemical (pesticide, perfumes, paint, car exhaust). Extreme symptoms occurred in 15%. My hypothesis is the cacosmia is a symptom of time dependent sensitization to chemicals in the environment.

I divided the group into how sensitive they were on cacosmia and how sensitive they were to wheat, dairy products, and eggs. I found that the tendency to get sick with drugs like alcohol, codeine and morphine was significantly higher in the people who had trouble with foods and chemicals.

I asked another group of 643 college undergraduates to relate the frequency of their symptoms, without any relation to drugs, and I did a step-wise multiple regression analysis on the results. There was significantly more memory complaint in the people with food and chemical problems, even after controlling for depression and gender effects. And another group of older people who had problems with chemicals and foods had more difficulty concentrating compared with people who did not, when controlled for differences in anxiety and age. When we measured the memory performance of 31 older people, depression accounted for a little over one-quarter of the variance in their immediate memory. We looked at the delayed and recognition memory pattern that goes with a dementia-like picture and found that olfactory-identification ability (OLF) and cacosmia (CAC) accounted for large parts of the variance (respectively, delayed: OLF 23%; CAC 22%; recognition: OLF 15%; CAC 33%). These two factors did not correlate well, only at the 0.3 level, so they cannot be the same. The findings suggest that cacosmia may be associated more with a dementing process.

To differentiate CS from affective disorders, the first step is to eliminate major depressive disorders. The second is to do chemical testing in a controlled environment. The third is to do neuropsychological tests and tests for gait and balance disturbances and spatial abnormalities, all of which are not usually seen in people who are depressed. Finally, studies such as PET and SPECT scans and quantitative electroencephalogram to allow examination of the subtle effects of chemicals on the functioning brain might be done.

Remember that finding CS doesn't rule out psychological factors. Since these things cross-sensitize, it's likely that if people started out depressed, they will be more likely to show

sensitivity to chemicals. It's not an either/or situation; it's a both/and.

Question from Dr. Claudia Miller: When you refer to one-quarter of your group having "depression", what do you mean?

Dr. Iris Bell: We used a subscale of a psychological questionnaire called the Weinberger Adjustment Inventory. We're also using the SCL-90. These are self-report standardized measures of depression. I'm not talking about clinical levels of depression. Less than 1% of our people had that diagnosis. But it provides more information about the potential interaction between chemicals and stress.*

Dr. Claudia Miller: So when you say symptoms may be accounted for by depression in part, do you mean that depression may have origins in chemical exposure, because the instruments are not differentiating what the etiology of that depression is?

Dr. Iris Bell: Right.

* SCL-90 -Symptom Check List, Derogatis, L. (1977).

8. BIOLOGICAL MARKERS IN MULTIPLE CHEMICAL SENSITIVITIES: Eric Nisbet-Brown, MD, PhD

We used the Cullen definition (see page 18-19) to evaluate 47 patients referred with a diagnosis of Multiple Chemical Sensitivities (MCS), and we used criteria similar to those used by Dr. Nancy Fiedler to exclude those with psychiatric and medical diagnoses. We evaluated 42 females and 5 males with an age range from 24 to 67 years. All were Caucasian. Forty-five lived in urban areas, averaged 15.5 years of education, and had had symptoms for an average of 1.9 years.

Seventeen patients were excluded with psychiatric diagnoses, and 19 were excluded for medical reasons. Of the remaining 11, only 5 had an identifiable single precipitating event or illness.

We did a standardized work-up covering medical, occupational, and medication history, and any history of atopy. We also did laboratory studies including a hemogram, routine biochemistry, urinalysis, thyroid function testing, screening for autoimmune diseases, immunoglobulin quantitation, and measurement of IgG subclasses. We looked at responses to tetanus, diphtheria, and polio immunizations and for evidence of infection with Epstein-Barr virus. As well, we did a number of specialized tests, including T and B cell phenotyping, Candida and Schick tests, and in vitro T and B cell proliferative responses to mitogens and recall antigens. We have also done preliminary studies to look at interleukin I and II production in vitro, complement activity and anti-smooth muscle and anti-parietal cell antibodies.

Patients had chest and sinus x-rays, pulmonary function tests, nasal air flow studies, and neurological testing as appropriate.

We found there were more patients in the medically excluded group with significant levels of antinuclear antibody, antithyroid antibody, antithyroglobulin, and antimicrosomal antibodies reflecting the presence of patients with these diseases in the excluded group. Similarly, high levels of serum IgE (≥ 100 micrograms/litre) were more common in the medically excluded patients. There were no differences in immunological functions between the case and either of the excluded groups, looking at cellular immune function, T and B-cell subsets, or autoantibody studies. For the markers of cell-mediated immunity, the ranges for all groups overlap extensively.

MCS and MCS-like subjects did not appear to have definable immunologic abnormalities, although the numbers in our study were small.

Comment by Dr. Nicholas Ashford: *This study shows the need to distinguish patient investigations from event-driven investigations. If there is a large neurotoxic event which is causing the immune system dysfunction, as opposed to a primary damage to the immune system, there may be very different types of biomarkers. The markers for*

biotoxicity may be very hard to find.

Dr. Eric Nisbet-Brown: We've attempted to define a pure population of MCS patients using conventional criteria. We felt that by excluding conventional illnesses we'd be able to pick up other abnormalities. We're looking for validated markers which will specifically identify MCS.

9. THE ENVIRONMENTAL CONTROL UNIT IN DIAGNOSIS: Gerald Ross, MD, CCFP, DIBEM, FAAEM

The environmental unit is an attempt to control "the total load" which is the cumulative effect of all the stressors that a person must adapt to, detoxify, or cope with in some manner. The total load includes things like chemicals, foods, inhalants, microbes, physical phenomena, genetic factors, nutritional deficits, and emotional stress.

The Environmental Control Unit at Tri-City Hospital in Dallas and the Environmental Health Centre in Dallas both have strict regulations against the use of pesticides or other pollutants. The walls and ceilings are made of porcelain on steel, and the floors are terrazzo tile. The furniture is either solid wood or metal, and the padding on the chairs is untreated cotton. All the air is filtered to remove both particulates and chemicals. The computer equipment is enclosed in a stainless steel box and gases are evacuated through a charcoal filter to scavenge solvents and hot plastic fumes.

Patients in the Occupational and Environmental Unit at Tri-City Hospital in Dallas drink spring water which is bottled in glass, and they consume organically grown foods. They sleep on mattresses made from layered cotton blankets.

The evaluation of Chemical Sensitivity (CS) begins with a thorough environmental history and intradermal and inhalation testing. The bipolarity of the response discussed earlier by Dr. Miller is controlled by admitting the patient to an environmental unit, which minimizes all the extraneous factors and independent variables which can lead to inaccurate results. Patients are challenged, one at a time, to the foods and chemicals which are being investigated using intradermal tests or rotational diets.

Double-blind inhalant challenges are done in a totally sealed booth, with exposure to concentrations so low they are below the odour threshold. Water is used as a placebo control, and if a patient is de-adapted, reliable data can be obtained.

Patients can also be assessed with a binocular iris corder, developed by Hamamatsu Photonics in Japan. Patients are dark adapted (light de-adapted) for 15 minutes and a measured pulse of light is shone into their eye. A computer measures the contraction and recovery of the pupil in response, which is a precise assessment of the function of the autonomic nerve response. Measurements are made before and after double-blind inhalation challenges, and sometimes before and after intradermal challenges and electromagnetic challenges as well. We frequently find that CS patients have an instability in autonomic nerve function, both at baseline and after challenge.

Recently we have been using triple-headed SPECT (single photon emission computed tomography) scans in CS patients with neurocognitive problems, which scan gives a metabolic or functional pattern of biochemical activity in the brain. When CS patients are scanned before and after chemical exposure, SPECT scans frequently show a neurotoxic pattern of injury which is distinctly different from that seen in psychiatric diseases and Alzheimer's. This suggests there are physiologic correlates to the "brain fog" and the memory problems and the mood instability and other central nervous system (CNS) symptoms CS patients have been reporting.

We have now looked at 80 CS patients; 85% have an abnormal scan. We have looked at 22 breast implant patients who have neurocognitive problems, and 21 have abnormal scans. We have looked at 15 normal healthy individuals; 12 have normal scans and 3 have minimal abnormalities which take them out of the normal range. We have not yet done

challenges on normals, and follow up over time needs to be done. However, we have done follow-up on 10 patients who have undergone a detoxification program and there is significant improvement in the neurotoxic metabolic activity on their scans.

Comment by Dr. James Day: *I'm concerned that control studies have not been done.*

Dr. Gerald Ross: *You're quite right. We do need to do controlled challenge studies on normals. The difficulty is that triple-headed SPECT scans are expensive, but that work is underway.*

Comment by Dr. Arthur Leznoff: *It would be fascinating if you could do a Pavlov's dog experiment and SPECT scan the dog before and after you rang the bell.*

Dr. Gerald Ross: *Perhaps there is an element of Pavlovian conditioning in some CS patients. I warn them not to assume that when they smell something they will necessarily react to it. I have observed cases that I felt were overreacting from a "psychological component". In these situations, I have used psychotropic medications where I thought it was appropriate, and I have sometimes referred patients for psychiatric care.*

REPORTS FROM THE WORKING GROUPS

1. DIAGNOSTIC STATEMENT GROUP: Lynn Marshall, MD, FAAEM, Chairperson and Rapporteur*

I. Diagnosis in General Terms

"Diagnosis" is "the determination of the nature of a disease"(1). Is Multiple Chemical Sensitivities (MCS), a relatively recently observed clinical phenomenon, a "disease"? The consensus of this group was that, even though we do not yet fully understand its mechanisms and etiology, MCS certainly meets the following dictionary definition of a "disease": "A condition of an organ, part, structure, or system of the body in which there is incorrect function resulting from the effect of heredity, infection, diet or environment" (2).

Diagnosis is used for clinical and research purposes. Clinically, diagnosis is useful to the individual with a disease because it allows a clinician to attach a name to the ailment, offer a prognosis (if the natural history of the disease is known), devise a treatment plan, and, when appropriate, assist the patient in applying for compensation or sickness benefits.

In research, diagnosis leads to study of the natural history, prevalence and etiology of a disease (as well as the most effective diagnostic and treatment methods).

The particular diagnosis that is proffered often depends on the part of the health care system the patient accesses. Patients may seek help because of psychosocial distress resulting from (biological) illness, and thus be more likely to receive a psychiatric diagnosis. It is also possible that MCS-like symptoms could be the psychophysiological manifestations of psychosocial distress. In any case, compassion for patients is essential, as is competence in establishing a diagnosis. Whether a diagnosis is to be used for clinical or research purposes, it should satisfy clear definitional criteria.

II. MCS Definition for Clinical Purposes

Various case definitions of MCS, which share many common features, were discussed. Adoption of the Thomson Committee definition (Appendix 1:1), now used by the World Health Organization, and the National Research Council (NRC) definition was suggested (Appendix 1:2). Cullen's definition (Appendix 1:3), although more restrictive than the others, would be more useful if it were modified to read "symptoms are *sometimes* acquired in relation to some documentable exposure(s), insult(s), or illness(es)." Also discussed were Ashford/Miller's criteria (Appendix 1:4), Randolph's early description (Appendix 1:5), and Davidoff's criteria (Appendix 1:6). Davidoff's criteria were developed on the basis of results of a survey of 86 occupational physicians, allergists, and environmental physicians, each of whom had seen 10 or more MCS-like patients. The components of proposed definitions/descriptions are summarized in Table 1.

A problem with all the current definitions is that patients who meet some of the criteria for MCS may (at least initially) be unaware of whether or what environmental exposures provoke symptoms. Hence, family physicians need to be vigilant for multiple office visits/referrals, even for markedly different complaints. The group agreed that a key feature clinically is improvement of symptoms when certain exposures are not encountered or are avoided, and that it is important to state when there is any suspicion of MCS, so that both physician and patient will begin to look for environmental contributors.

There is a good precedent for diagnostic decision-making in systemic lupus erythematosis. If all clinical criteria are met, then the diagnosis is "hard". If not, then a "soft" diagnosis is made with a decreasing scale from "probable" to "possible" to "unlikely".

The consensus was that individuals whose conditions fit the characteristics outlined in the NRC definition should be considered "possible"

* Rapporteur's additions are bracketed for clarification

MCS cases for clinical purposes. Improvement following reduction or elimination of suspected exposures and recurrence of symptoms on re-exposure would make the diagnosis "more probable". Individuals who responded to double blind challenge(s) in a controlled environment such as an Environmental Control Unit (ECU), after an appropriate interval for deadaptation, would be "most probable" cases, although the majority of group participants felt that such cases could be called "confirmed".

If a "possible" or "probable" diagnosis of MCS were made, other known diagnoses that could account for the symptoms should be identified, generally effective treatment(s) applied, and any retained symptoms monitored. However, if MCS coexisted with a known diagnosis, there was concern that conventional treatment could at best be mildly effective and at worst could exacerbate symptoms. While some available tests offer useful background data, and there are promising new tests such as SPECT (single photon emission computed tomography) scans, it would be very helpful to have some specific diagnostic tests formally validated as to their ability to distinguish a spectrum of cases.

III. MCS Definition for Research Purposes

Several different research approaches have been applied. Davidoff is presently accepting clinicians' diagnoses of MCS and then characterizing the individuals so diagnosed. Another approach is to use a broad definition (such as that proposed by NRC) and thus include a large sample, paring to subgroups for characterization. Cullen set a restrictive definition and then studied a smaller sample meeting narrower criteria. It was suggested the narrow criteria method might be more useful until there is better data on MCS, although there are advantages and disadvantages to each approach.

A reasonable next step might be decision by a panel of experienced clinicians on most likely and least likely cases using definitional criteria and documentation of history, physical examination, and laboratory tests. The Centers for Disease Control in the United States are following a similar process regarding chronic fatigue syndrome.

Participants concurred that MCS definitional issues are complex and that needs/objectives are different from clinical and research points of view.

Table 1: Components of Proposed MCS Definitions

More Common (Appendix Numbers)	Less Common (Appendix Numbers)
Chronic symptoms (1,5,6)	Recurrent Symptoms (3)
Multisystem involvement (1,3,5,6)	Acquired disorder (3,5)
Symptoms provoked or worsened with exposures (1-6)	CNS involvement (1,5)
Unrelated substances provoke (1,3,5,6)	Varying morbidity (1,5)
Exposures provoke symptoms at levels tolerated by the majority of the population (1-3,5,6)	Addiction type responses (5)
Symptoms improve or disappear with nonexposure/avoidance (1,2,4-6)	Spreading of incitants (5)
No single predictive diagnostic test (1,3,5,6)	Comorbid conditions (2)
	Symptoms elicited by demonstrable exposures (3)
	No consistent physical findings (1,5)
	Diagnosis by challenge after interval under strict environmental control (4,5)

2. RESEARCH STATEMENT:
Eric Nisbet-Brown, MD, PhD, Chairperson and Rapporteur

The objectives of the group session were to formulate recommendations regarding further research into Multiple Chemical Sensitivities (MCS) and to advise on research priorities. Due to the general lack of scientific knowledge on MCS as a whole, research issues discussed in the session covered a wide range of areas including clinical diagnosis, case definition, etiologic and biologic mechanisms, epidemiology, and prevention and treatment. Several recommendations were drafted prior to the workshop by the chairperson, with the assistance of Dr. Cecil Collins-Williams (Hospital for Sick Children, Toronto) and Dr. Gail Eyssen (the Department of Preventive Medicine and Biostatistics, University of Toronto), to address the objectives. These recommendations were presented to the participants of the session, vigorously discussed, and subsequently revised to reflect consensus within the group.

I. Recommendations Concerning Clinical Diagnosis:

(1) A strategy should be developed for the identification of categories of persons with increasing likelihood of having MCS based on clinical criteria. Approaches to this should include the development and evaluation of a questionnaire to identify cases with exposures and symptoms believed to be compatible with MCS. Other strategies including standardized medical, occupational, exposure, and psychiatric histories; and uniform criteria for physical examination should also be considered.

(2) Diagnostic algorithms should be developed for excluding other diseases in persons presenting with symptoms which may be confused with MCS.

(3) A psychiatric interview by a psychiatrist or psychologist with an interest in psychodynamics should be a part of the workup.

(4) An environmental control unit or any other method which helps to assess the response of a patient under exposed and non-exposed conditions may be an appropriate part of the diagnostic work up.

(5) The validity and appropriateness of these approaches must be determined by groups with expertise in immunology and allergy, clinical ecology, epidemiology, toxicology, respirology, endocrinology, occupational medicine, psychiatry, and psychology.

II. Recommendations On Diagnostic testing:

(1) A panel of diagnostic tests which may be useful in the evaluation of patients with symptoms suggestive of MCS should be developed and assessed for sensitivity and specificity in diverse patient and control groups. Areas to be considered include routine hematologic and biochemical studies, specialized tests of cellular and humoral immune function, endocrine function, and neurological function.

(2) The role of neurological and psychiatric assessment with specialized psychological and neurological testing must be defined.

(3) The value of specialized imaging studies, including MRI (magnetic resonance imaging) and brain scan should be evaluated.

(4) The role of time factors in causing sensitization and eliciting responses should be assessed.

(5) The validity of methods used by clinical ecologists to test patients with MCS must be assessed.

(6) The sensitivity and specificity of tests should be determined under appropriate experimental conditions in patients judged to have MCS by the clinical criteria established above and by criteria applied by the clinical ecologists. One approach would be to evaluate adaptation/de-adaptation as a possible model.

(7) The validity of new or alternative methods of diagnostic testing, including high resolution

SPECT (single photon emission computed tomography) or PET (positron emission tomography) scanning, basophil degranulation, measurement of chemical antibodies, autoantibodies, and concentrations of toxins in blood, hair, and urine samples should be confirmed by determining the sensitivity and specificity of these tests in relation to clinical criteria.

(8) Placebo-controlled double blind studies of therapeutic efficacy should be conducted where appropriate and appropriate control groups should be included.

(9) Cross-over studies in which patients serve both as their own experimental subject and control may be appropriate in some circumstances.

(10) Any tests which appear to have validity in establishing a diagnosis of MCS should be studied for reproducibility in clinical settings.

III. Recommendations On the Case Definition:

(1) A major goal must be to establish a case definition(s) for MCS with validity for diagnostic, research, epidemiologic, and treatment purposes.

(2) Validated and reproducible diagnostic tests should be used in conjunction with clinical diagnostic criteria to develop the case definition. Definitive trials of diagnosis and treatment efficacy would be facilitated by an adequate diagnosis of MCS.

(3) The relation of MCS to other disorders must be assessed.

IV. Recommendations On Etiologic and Biologic Mechanisms:

(1) The etiology of MCS can be examined in terms of environmental, social, and biological risk factors for disease. Environmental and social risk factors for MCS could be identified by comparing case and non-case groups for suspect exposures prior to disease onset.

(2) When specific factors have been identified, cohort studies could be undertaken to determine risk associated with exposure.

(3) Clinical trials could be undertaken to identify the biological effects of exposure and hence to understand the mechanisms of the disease process. The development of animal systems or other experimental models may assist in this process.

V. Recommendations On The Prevalence and Dynamics of the Disease:

(1) Using the clinical and diagnostic criteria described above, it should be possible to assess the prevalence of MCS in a variety of clinical settings and in the population at large.

VI. Recommendations On Treatment:

(1) Therapies currently used by clinical ecologists, including avoidance, should be evaluated. New therapies which become available must be evaluated.

VII. Recommendations On Prevention:

(1) When risk factors for MCS have been identified, preventive strategies must be proposed and evaluated.

(2) Education programs for health practitioners and affected populations must form part of any preventive strategy.

Comment from Dr. Nicholas Ashford: *I was a member of the research statement workshop, and what the chairman has reported represents a unanimous agreement among the members. However, the record should also show that there was substantial agreement on three other points:*

First, examination of event-driven studies (a sick building, a pesticide spill, or a collection of patients with a history of exposure) would be fruitful.

Second, the environmental unit should be considered as a possible candidate as the gold standard for the diagnosis of MCS.

Third, we should acknowledge the connection

between asthma and rhinitis and MCS.

Dr. Claudia Miller: *There have been three major meetings on this subject and not a lot of progress has been made. One of the major areas of movement that need to be made is the establishment of a registry, not by establishing a definition of a template, but rather by asking all individuals who feel they are chemically sensitive to identify themselves and say what symptoms they are having in a simple way, and what kind of exposures they attribute those symptoms to. There's been a major increase in the use of pesticides, and if indeed it is one of the major triggers for this problem, then we need to find ways to intervene and do it soon in the interest of public health.*

APPENDIX A:

LIST OF SPEAKERS

Barry Jones, MD, FRCPC - Workshop Chair,
Director, Schizophrenia Program,
Royal Ottawa Hospital;
Associate Professor,
University of Ottawa,
Ottawa, Ontario.

Susan Abbey, MD, FRCPC
Psychiatrist;
Director, Psychosomatic Medicine Program,
The Toronto Hospital;
Assistant Professor,
Department of Psychiatry,
University of Toronto,
Toronto, Ontario.

Nicholas Ashford, PhD, JD
Chemist and Lawyer;
Professor of Technology and Policy,
Massachusetts Institute of Technology,
Cambridge, Massachusetts, USA.

Iris Bell, MD, PhD (Neurophysiology)
Psychiatrist;
Assistant Professor,
College of Medicine,
Department of Psychiatry,
University of Arizona Health Sciences Centre,
Tuscon, Arizona, USA.

Nancy Fiedler, PhD
Psychologist;
Assistant Professor,
Division of Occupational Medicine,
Environmental and Occupational Health Sciences Institute,
Robert Wood Johnson Medical School,
Piscataway, New Jersey, USA.

Roy Fox, BSc, MD, FRCPC, FRCP, FACP
Fellow of Dalhousie University at Environmental Health Centre - Dallas;
Professor of Medicine,
Dalhousie University, Nova Scotia;
Former Director of Centre for Health Care of the Elderly,
Camp Hill Medical Centre,
Halifax, Nova Scotia.

Arthur Leznoff, MD, FRCPC
Allergist and Immunologist;
Head, Division of Clinical Immunology,
St Michael's Hospital, Toronto;
Associate Professor of Medicine,
University of Toronto,
Toronto, Ontario.

Lynn Marshall, MD, FAAEM
Environmental and Occupation Physician;
President, Canadian Society for Environmental Medicine,
Ottawa, Ontario.

Claudia S. Miller, MD, MS
Allergist and Immunologist;
Assistant Clinical Professor,
Allergy and Immunology,
Health Science Centre,
University of Texas,
San Antonio, Texas, USA.

Eric Nisbet-Brown, MD, PhD
Immunologist;
Consultant to the Ontario Ministry of Health;
Director of Clinical Immunology,
The Toronto Hospital,
Toronto, Ontario.

Gerald Ross, MD, CCFP, DIBEM, FAAEM
Physician,
Environmental Health Centre,
Dallas, Texas;
Medical Director,
Nova Scotia Environmental Medical Clinic,
Victoria General Hospital,
Halifax, Nova Scotia;
Consultant to the Ontario Ministry of Health.

Note: The following list reflects positions and titles held by the speakers at the time of the workshop.

Dr. Susan Abbey
Department of Psychiatry
Toronto General Hospital
8 EN-219 Elizabeth Street
Toronto, Ontario
M5G 2C4

Sven Anderssen
R.R. #4
Kemptville, Ontario
K0G 1J0

Dr. Jim Argo
c/o Laboratory Centre for Disease Control
Health Canada
HPB Building
Ottawa, Ontario
K1A 0L2

Dr. Nicholas Ashford
Professor of Technology and Policy
Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Susan Baxt
143 Champlain Street
Hull, Quebec
J8X 3R1

Dr. Iris Bell
Department of Psychiatry
University of Arizona
Health Sciences Centre
1501 North Campbell Avenue
Tucson, Arizona 85721

Mr. Denis A. Bourque
Head, Office of the Director General
Atmospheric Research Directorate
Environment Canada
4905 Dufferin Street
Downsview, Ontario
M3H 5T4

Dr. Irving Broder
Chairman
Gage Research Institute
223 College Street
Toronto, Ontario
M5T 1R4

Dr. J. Broffee
Occupational Health Clinics of Ontario Workers
848 Main Street East
Hamilton, Ontario
L8M 1L9

Dr. Peter Cairns
Biosafety Officer
Agriculture Canada
3851 Fallowfield Road
Nepean, Ontario
K2H 8P9

Mrs. Margaret Carter-Rhéaume
492 Athlone Avenue
Ottawa, Ontario
K1Z 5M8

Ms. Monique Charron
Health Policy Development Section
Room 2068
Health Canada
Jeanne Mance Building
Ottawa, Ontario
K1A 0K9

Rosemary Clarke
Environmental Health Unit
Health Canada
C225, Tupper Building
Confederation Heights
Ottawa, Ontario
K1A 0M2

Dr. C. Collins-Williams
1 Aberfoil Crescent
Etobicoke, Ontario
M8X 2X8

Sandra Comeau
1593 Prestwick Drive
Orleans, Ontario
K1E 2E6

Dr. Greg Cook
Alcohol and Drug Section
Provincial Health Officer
Ministry of Health
7-1, 1515 Blanchard Street
Victoria, British Columbia
V8W 3C8

Note: While every effort has been made to present an accurate list of participants, we are aware that the names of a few who attended are not available. We regret any inconvenience caused by this omission.

Dr. John W. Davies
Laboratory Centre for Disease Control
Health Canada
Ottawa, Ontario
K1A 0L2

Dr. James Day
76 Stuart Street
Kingston, Ontario
K7L 2V7

Mirella DeMarinis
Health Safety and Security
Health Canada
1350 Jeanne Mance Building
Ottawa, Ontario
K1A 1B4

Asha DeSa
Terminal P.O. Box 8051
Ottawa, Ontario
K1G 3H6

Ms. Estelle Drolet
17 Andrea Crescent
Nepean, Ontario
K2J 1G8

Ms. Barbara Dubuc (Brady)
Mental Health Division
Health Programs and Services Branch
Health Canada
Ottawa, Ontario
K1A 1B4

Dr. C. Edward-Ellis
Canadian Public Health Association
Associate Medical Officer
Regional Municipality of Ottawa-Carleton
495 Richmond Road
Ottawa, Ontario
K2A 4A4

Dr. Nancy Fiedler
Robert Wood Johnston Medical School
Department of Environmental and Community Medicine
681 Frelinghuysen Road
EOHSI Building, Room 210
Piscataway, New Jersey 08855

Dr. G. Finlayson
Box 421
Caledon, Ontario
L0N 1C0

Dr. Roy Fox
Victoria General Hospital
Environmental Medicine Clinic
Bethune Building
Room 520
1278 Tower Road
Halifax, Nova Scotia
B3H 2Y9

Mr. John Gayton
Public Works and Government Services
Room D304 - Sir Charles Tupper Building
Riverside Drive
Ottawa, Ontario
K1A 0M2

Dr. John Gerrard
Paediatrics
University of Saskatchewan
809 Colony Street
Saskatoon, Saskatchewan
S7N 0S2

Dr. Jean-Yves Gosselin
President
Canadian Psychiatric Association
200 - 237 Argyle Street
Ottawa, Ontario
K2P 1B8

Ms. Gweneth Gowanlock
Director, Mental Health Division
Health Programs and Services Branch
658 Jeanne Mance Building
Health Canada
Ottawa, Ontario
K1A 1B4

Ms. Fabienne Grange
R.R. #1
St. Clements, Ontario
N0B 2M0

Dr. T. Gregor
1111 Prince of Wales Drive
Ottawa, Ontario
K2C 3T2

Dr. Paul Groff
Royal Ottawa Hospital
1145 Carling Avenue
Ottawa, Ontario
K1Z 7K4

Mr. J. Vincent Guenette
6395 Lumberman Way
Orleans, Ontario
K1C 1V8

Claudette F. Guibord
Advocacy Group for the Environmentally Sensitive
1887 Shaine Court
Orleans, Ontario
K1C 2W6

Dr. S. Gupta
Monitoring and Criteria Division
Environmental Health Centre
Bureau of Chemical Hazards
Health Canada
Ottawa, Ontario
K1A 0L2

Jo Anne Hall
c/o Louise Lorrain
Occupational Health Unit
Medical Services Branch
Agriculture Canada
K.W. Neatby Building
960 Carling Avenue, B16
Ottawa, Ontario
K1A 0C5

Ms. Louise Hall
Head, Health and Safety Section
Public Service Alliance of Canada
33 Gilmour Street, Suite 901
Ottawa, Ontario
K2P 0P1

Dr. Douglas Henshaw
Mental Health Services
Department of Health
Joe Howe Building
1690 Hollis Street
P.O. Box 488
Halifax, Nova Scotia
B3H 2R8

Dr. Byron Hyde
121 Iona Street
Ottawa, Ontario
K1Y 3M1

Ray Jackson
208 Clemow Avenue
Ottawa, Ontario
K1S 2B4

Jeannette Jeffreys
2574 Chambers Avenue
Ottawa, Ontario
K2B 7S2

E. Johnston
Environmental Hypersensitivity Association of Ontario
P.O. Box 27545
Yorkdale Postal Outlet
Toronto, Ontario
M6A 3B8

Dr. Barry Jones (Workshop Chair)
Royal Ottawa Hospital
1145 Carling Avenue
Ottawa, Ontario
K1Z 7K4

Mr. J. Kassirer
Marketing director
Green Eclipse Incorporated
2269 Concession # 4
R.R. # 1
Goodwood, Ontario
L0C 1A0

Dr. John Kirkbride
Director
Occupational Health Unit
Medical Services Branch
Health Canada
11th Floor, Jeanne Mance Building
Ottawa, Ontario
K1A 0L3

Joan Klein
Allergy and Environmental Health Association
P.O. Box 31323
Halifax, Nova Scotia
B3K 5V5

Anne O'Driscoll
15 Gwynne Avenue
Ottawa, Ontario
K1Y 1X1

Barbara Ouellet
Director, Health Service Systems
Health Canada
662 Jeanne Mance Building
Ottawa, Ontario
K1A 1B4

Anne Louise Parker
#10 - Burnham Road
Ottawa, Ontario
K1S 0J8

Joanne Parker
Environmental Hypersensitivity Association of Ontario
Box 585, Station K
Toronto, Ontario
M4P 2H1

Mr. Edward J. Pennington
Executive Director
Canadian Mental Health Association
2160 Yonge Street, 3rd Floor
Toronto, Ontario
M4S 2Z3

Mr. Robert Phripp
R.R. #1,
St. Clements, Ontario
N0B 2M0

Dr. L. Pilon
Senior Medical Officer
Canada Pension Plan, Disability Operations Division
Income Security Programs
Health Canada
Ottawa, Ontario
K1A 0L1

Sandra Proudfoot
"The Farmer's Walk"
R.R. #5
Orangeville, Ontario
L9W 2Z2

Mr. Roger Pulver
24 Cayley Street
Dundas, Ontario
L9H 2E7

Dr. A. Reinhartz
Occupational Health Clinics for Workers
547 Victoria Avenue
Windsor, Ontario
N9A 4N1

Luis Rodriguez
Researcher
Canada Mortgage and Housing Corporation
700 Montréal Road
Ottawa, Ontario
K1A 0P7

Dr. A. Romaniuk
Senior Medical Officer
Canada Pension Plan, Disability Operations Division
Income Security Programs
Health Canada
9th Floor, Tower A
Vanier, Ontario
K1A 0L1

L. Rosborough
Ottawa District Health Council
955 Green Valley Crescent
Suite 350
Ottawa, Ontario
K2C 3V4

Dr. Gerald Ross
Environmental Health Centre of Dallas
205 - 8345 Walnut Hill Lane
Dallas, Texas 75231

L. Rotor
343 Roxdale Avenue
Orleans, Ontario
K1E 1T9

Docteur Jacques H. Roy
Directeur général
Services de la santé
Service correctionnel Canada
340 ouest, avenue Laurier, 2e étage
Ottawa, Ontario
K1A 0P9

Mr. Peter Russell
Research Division
Canada Mortgage and Housing Corporation
700 Montréal Road
Ottawa, Ontario
K1A 0P7

Ms. Virginia Salares
Project Manager
Canada Mortgage and Housing Corporation
Research Division
700 Montréal Road
Ottawa, Ontario
K1A 0P7

Mr. Roy Sampson
National Health Research and Development Program
Extramural Research Programs
Health Canada
2nd Floor, Tower A, Holland Cross
Ottawa, Ontario
K1A 1B4

Mr. Alex Saunders
Chief Executive Officer
Canadian Psychiatric Association
200 - 237 Argyle Avenue
Ottawa, Ontario
K2P 1B8

Mr. H. Schneiderman
Transport Canada
Place de Ville
AANFVC
Ottawa, Ontario
K1A 0N8

Ms. Brenda Shestowsky
Nursing Policy Consultant
Canadian Nurses Association
50 Driveway
Ottawa, Ontario
K2P 1E2

Carol Silcoff
Mental Health Division
Health Canada
652 Jeanne Mance Building
Ottawa, Ontario
K1A 1B4

Dr. Bruce Small
President
Green Eclipse Incorporated
2269 Concession no. 4
R.R. # 1
Goodwood, Ontario
L0C 1A0

Ms. Elizabeth Stutt
Allergy and Environmental Health Association
Ottawa Branch
P.O. Box 33023
Nepean, Ontario
K2C 3Y9

Kathryn Sullivan
Children's Mental Health Unit
Mental Health Division
Health Canada
650 Jeanne Mance Building
Ottawa, Ontario
K1A 1B4

Fernande Surprenant
Occupational Therapy Program
University of Ottawa
451 Smyth Road
Ottawa, Ontario
K1H 8M5

Dr. Gordon Sussman
Society for Allergy and Clinical Immunology
202 St. Clair Avenue
Toronto, Ontario
M4V 1R2

Mr. Brian Sutherland
Regional Manager
Ministry of Housing of Ontario
1365 Richmond Road
Suite 300
Ottawa, Ontario
K2B 6R7

Dr. Lisa E.A. Taylor
Safety Officer
Animal Disease Research Institute
Agriculture Canada
3851 Fallowfield Road
Nepean, Ontario
K2H 8P9

Dr. Michael Teehan
Deputy Chief
Department of Psychiatry
Camp Hill Medical Centre
1763 Robie Street
Halifax, NS
B3H 3G2
and
Representative
Medical Research Council Board
Tower B, Holland Cross
5th Floor, 1600 Scott Street
Ottawa, ON
K1A 0W9

Lan Chi Nguyen Thi
Interior Environment Engineer
Public Works and Government Services
Sir Charles Tupper Building
Riverside Drive, E540
Ottawa, Ontario
K1A 0M2

Mr. George White
Central Plant Health Laboratory
3851 Fallowfield Road
Nepean, Ontario
K2H 8P9

Dr. Valerie Wilmot
R.R. #4
Kemptville, Ontario
K0G 1J0

Dr. Tom Wood (Editor)
Respirologist
Respirology
St. Joseph's Health Centre
268 Grosvenor Street
London, Ontario
N6A 4V2

APPENDIX C:

SPEAKERS' PAPERS

CHEMICAL SENSITIVITY - THE CLINICAL PICTURE

Roy A. Fox

Sensitivity is defined as the state or quality of being sensitive or it is the ability of an organism or part of an organism to react to stimuli. It is also referred to as a state of irritability. The term chemical sensitivity (C.S.) is used to describe an abnormal state of health characterised by intensified and adverse responses to components found in food, water, air or physical surroundings of the patient's environment (Hileman 1991). Rea (1992) has defined it as an adverse reaction(s) to ambient levels of toxic chemical(s) contained in air, food and water.

The nature of the adverse reaction determines the clinical picture. As the clinical picture is described it will become clear that the life of a person with C.S. becomes dominated by "reactions". The nature of these reactions as perceived by the patient will be described later. There are many factors which influence the adverse reactions, for example the tissue or organ involved, the chemical and pharmacological nature of the environmental incitant, its concentration and toxicity and the length of time exposed to it. Individuals vary in their susceptibility, which may be related to their nutritional state and their genetic constitution. The toxic load of ambient chemicals helps determine the ability to detoxify, a high load providing competitors for the detoxification pathways. Other stressors would add to the total load on the patient and contribute to the nature of the response and the type of reaction.

It is not surprising that the clinical picture of C.S. is so varied. Despite this variability there are many similarities between patients and a characteristic pattern of symptoms and signs allows recognition and accurate diagnosis.

ESTABLISHING A DIAGNOSIS:

A number of investigators have attempted to define Chemical Sensitivity with varying degrees of success. Many refer to the condition as Multiple Chemical Sensitivities (Cullen 1987, McLellan 1991, Ashford and Miller 1992). For purposes of study it is clearly important to have agreed upon criteria but at this stage of our understanding they need to be sufficiently wide to include the majority of cases. In terms of the clinical picture it is better to think of C.S. as a state of altered reactivity or of altered health which can and should be diagnosed before the onset of tissue damage or end organ disease. It can and does exist along with a variety of well recognised and diagnosable syndromes, pathological states or clearly defined diseases. For example asthma, acne, fibromyalgia or irritable bowel syndrome. In order to diagnose this altered state of reactivity certain features should be present:

1. Symptoms are usually present in more than one organ system, although in early cases a single system is involved.
2. Symptoms are distressing and recur with environmental exposure. The symptoms may vary with exposure and over time.
3. Symptoms become chronic and by the time a physician is consulted have usually been present for 6 months.
4. Symptoms are elicited by exposure to ambient concentrations of substances which do not normally produce illness in others.
5. Most symptoms, particularly those of a reaction, lessen or disappear over time, after removal from the incitant.
6. Symptoms cannot be explained by any other specific etiological diagnosis, for example bacterial infection.

These criteria fit very closely with the criteria agreed upon in a workshop of the Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council (1992). Although I have defined C.S. as altered reactivity it does fulfil the definition for a disease (Webster 1989).

PRESENTATION:

The presentation of C.S. is varied. It may take a long time for the patient to become aware that something is amiss, and it may take several months

identify that they are reacting to foods. A few patients gain weight but the majority lose weight and for many there is a marked weight loss. It is thought that continued exposure to chemically contaminated food continues to damage the gastrointestinal mucosa leading to increased permeability, and thus increased exposure to a variety of potential immunogens and toxins. This damage also results in failure to absorb an adequate amount of nutrients.

One of the first and most obvious target organs for many patients is the skin. A variety of skin rashes may be identified including an acne like eruption, necrotizing folliculitis, a lupoid rash, worsening of eczema or the onset of urticaria. Many complain of dry skin. which is often severe, and this is usually associated with marked pruritus. The genitourinary system might appear to be an unlikely target, but urinary complaints of frequency and nocturia are common. This may be extreme and lead to incontinence of urine. Many female patients will complain of premenstrual symptoms or a worsening of any of their symptoms at that time of their cycle. Other disturbances of menstruation will also occur including changes in the character or the extent of flow. Another very common if not universal complaint amongst the sufferers of C.S. is a significant deterioration or even loss of libido.

Examination of the patients with C.S. will usually not reveal any pathognomonic features. The findings will depend upon the organ affected (the target organ) and the nature of the exposure. The majority of patients have postural instability and demonstrate an inability to stand with feet together and eyes closed (Romberg's sign). A finding that fits with common complaint of dizziness. The skin should be examined carefully for the abnormalities which have been described above. In addition to these, many patients report new skin tags in various places and the skin of the face takes on an unhealthy corrugated appearance. There is often a yellow, almost jaundiced, appearance of the skin which has been referred to as the "chemical yellows". Other features which are frequently seen include edema of the face and extremities and the finding of black circles under the eyes. Vascular instability is a common feature and more than half the patients will show or give a history of easy bruising and petechiae. Vascular instability is presumably related to damage to the autonomic nervous system and one of the most distressing features of a reaction in the C.S. patient is cold sensitivity and cold extremities. The examining physician will usually find cold hands, and about a quarter will have Raynaud's phenomenon. The bruising may be related to coagulation disturbances but these are rare. Laboratory testing may reveal abnormalities of the blood count. Depressed white cell count is the most common abnormality but is only found in 15 to 20 per cent, anemia is less common. Other routine laboratory tests may be abnormal and in about a quarter there may be elevation of liver enzymes, specifically the transaminases which would indicate hepatocyte damage or inflammation. Tests of disturbed immune function may also be found to be abnormal but are not pathognomonic.

The clinical picture in the patients with established C.S. and prolonged exposure is one of constant ill health without remission. The patient is likely to have a combination of problems already discussed, the most prominent symptoms depending upon the target organs involved. Patients who are less ill or who have begun to correct their deficiencies are likely to have their lives dominated by reactions. The patient learns to identify those environmental factors that provoke a reaction and make them feel ill. There is no typical reaction since it will depend upon the incitant and the target organ as described above. A reaction to exposure to a sick building for example, might result in disturbed cognitive function or brain fog. The subject becomes aware that things are not working properly, and that it is difficult to think clearly or to remember names. There may be disordered perception, an inability to concentrate, postural instability or a significant mood swing. Many will develop a headache and become nauseated, and for some this is the first change to be noted in a reaction. There is frequently tingling of the extremities. For some, the reaction is characterised by the extremities becoming cold (vascular spasm) and then an inability to keep warm and to feel extremely cold. Uncontrolled shivering may occur. Such changes are thought to represent autonomic nervous system instability. The reaction may continue for some time after exposure and night sweats are another problem.

The outcome of such reactions described above are variable. Removal from exposure may result in rapid clearing. For others it will continue and they

will feel ill with persistent symptoms and associated fatigue for many hours. In some, brief exposure results in profound exacerbation of the skin rash or the development of mouth or nasal ulcers which will persist for days or weeks after exposure. Exposure to ambient chemicals can also provoke gut reactions, although food is more likely to do this. All of the features described are seen with food provocation, as well as sudden onset of cramps and diarrhea.

People with C.S. learn to avoid incitants as well as techniques to stop reactions. Some of these techniques appear strange but the experience of thousands of sufferers attest to their effectiveness.

CONCLUSION

The development of this altered state of reactivity or disease known as Chemical Sensitivity appears to be permanent in most cases. The current paradigm in Environmental medicine invokes the concept of Total Load. Therapy is aimed at reducing total load at the same time as replenishing nutritional deficits. With reduction of Total Load most people with C.S. improve. Their sensitivity diminishes, both in terms of number of incitants and in terms of magnitude of reaction. Those seen early in the course of their ill health improve sufficiently to lead an active life - with some minor modifications. The majority appear to retain their reactivity but at a lower level - many modifications to their lives are required but the sufferers learn to live with C.S. and develop effective coping skills. A minority continue to develop sensitivities and continue in a state of ill health, with a life dominated by severe reactions, leading to organ and tissue damage. The proportions in these groups, the reasons for the different outcomes and the best treatment approaches are not known at present and require further careful study.

REFERENCES

Ashford NA, Miller CS 1992 Chemical Exposures. Low Levels and High Stakes.

Cullen MR 1987 Workers with Multiple Chemical Sensitivities in M.R.Cullen ed. Occupational Medicine. State of the Art Reviews Vol.2 No.4 p655-661.

Hileman B (1991) Multiple Chemical Sensitivities. Chem.Eng.News 69(20); 26-42.

McLellan R 1991 Multiple Chemical Sensitivities (MCS). Overview and Future Directions. in Environmental Sensitivities Workshop. Supplement to Chronic Diseases in Canada ISSN 0228.8699 p17-20.

Rea WJ 1992 Chemical Sensitivity Volume 1. Lewis Publishers. Boca Raton. Ann Arbor. London. Tokyo.

Ross G.H. (1992) History and Clinical Presentation of the Chemically Sensitive Patient. Toxicology and Industrial Health 8; 21-28.

Webster 1989 Webster's Encyclopedic Unabridged Dictionary of the English Language, Portland House New York.

ACKNOWLEDGEMENT

I wish to acknowledge the encouragement and support of Dr G.H.Ross who has seen the sick patients at CHMC and shared the findings with me. I also acknowledge my fellow sufferers from Camp Hill Medical Centre who shared their experiences openly with me.

A CONTROLLED STUDY OF CHEMICALLY SENSITIVE PATIENTS

Nancy Fiedler, Ph.D.
Assistant Professor
Division of Occupational Medicine
Environmental & Occupational Health Sciences institute
681 Frelinghuysen Road
Piscataway, New Jersey 08855
(908) 932-0190

Howard M. Kipen, M.D., M.P.H.
Associate Professor
Division of Occupational Medicine
Environmental & Occupational Health Sciences Institute
681 Frelinghuysen Road
Piscataway, New Jersey 08855
(908) 932-0182

Presented At:

MULTIPLE CHEMICAL SENSITIVITIES AND THEIR RELEVANCE TO PSYCHIATRIC DISORDERS
Ottawa, Ontario
December 7, 1992

ABSTRACT

Chemically sensitive patients (MCS) report a broad range of symptoms in response to low levels of chemicals commonly encountered and tolerated. These symptoms have frequently been regarded as a reflection of psychopathology rather than due to chemical exposures. The purpose of the present study was: 1) to select chemically sensitive patients for study according to Cullen's (1987) criteria, and 2) to compare the psychiatric status of chemically sensitive patients with that of normal controls of comparable age, sex, and education. Results from this three year study indicated that 62% (23/37) of the patients referred for chemical sensitivity met the Cullen definition. Compared to normal controls, the chemically sensitive patients (N=23) did not have a significantly different rate of premorbid psychiatric disorder as determined by the Structured Clinical Interview for the DSM-III-R (4/23 for MCS; 2/18 for Normals). However, MCS patients had a significantly higher rate of current psychiatric diagnoses (4/23 vs. 0/18) than normal controls and had significantly more symptoms consistent with somatization disorder. The implications regarding causality of this disorder are discussed along with recommendations for future studies of the psychological factors involved in this disorder.

INTRODUCTION

Patients with chemical sensitivities report a variety of vague physical symptoms in response to low levels of chemicals tolerated by most individuals. The symptoms reported by chemically sensitive patients cannot be accounted for by any traditional laboratory test or physical diagnosis. Since environmental exposures and physical diagnoses are not present to a sufficient degree to account for chemical sensitivities, psychiatric diagnoses have been invoked as explanatory (e.g. Simon, 1990; Black, 1990; Brodsky, 1983). However, psychiatric diagnoses describe rather than explain symptoms. The purpose of the present paper is to present the demographics and psychiatric status of chemically sensitive patients selected according to specific criteria proposed by Cullen (1987). These patients have been compared to normal controls. A second purpose is to discuss appropriate controls for the study of chemically sensitive patients and to propose measures of behavioral traits that may contribute to these reactions. In contrast to traditional psychiatric diagnoses, assessment of behavioral traits should help us explain rather than simply describe these reactions.

Clearly, psychological factors play a role in all forms of illness (e.g. cancer) (Cheren, 1989) including chemical sensitivities. Therefore, the relevance of psychiatric factors in chemical sensitivities can be addressed at two levels. First, if chemical sensitivities does not exist independent of a premorbid psychiatric disorder, then it may represent patients who are searching for a more acceptable physical explanation for their long-standing psychiatric disorders. That is, a psychiatric disorder may put an individual at risk for developing chemical sensitivities. If the latter were the case, one would expect to find a higher rate of chemical sensitivities among various psychiatric groups (e.g. depression). Second, rather than operating as predisposing factors, psychiatric or behavioral factors may contribute to or exacerbate unusual sensitivities to chemicals (Schottenfeld, 1987). For example, based on an episode of illness or symptoms developing from exposures to chemicals (e.g. new carpet), particularly in situations expected not to produce illness, patients' fear could exacerbate responses to future exposures.

Whether as a premorbid or concurrent condition, psychiatric factors are an important aspect in the study of chemically sensitive patients. The first question we have addressed in our work is whether chemically sensitive patients, chosen according to the relatively rigorous and narrow criteria suggested by Cullen (1987), could be identified who did not have a premorbid psychiatric history (Fiedler et al., 1992). While other investigators (e.g. Black, 1990; Simon, 1990) have reported a significantly higher rate of premorbid psychiatric conditions among chemically sensitive patients, these investigators did not use equally rigorous criteria for patient selection. For example, one study used patients with environmental allergy, multiple chemical sensitivity or yeast disease (Black et al., 1990). When patients are selected based on Cullen's criteria, a different picture emerges in which premorbid psychiatric history does not appear to account for a majority of presentations of this problem (Fiedler et al., 1992; Fiedler, et al., in preparation). Nevertheless, certain behavioral characteristics may not be wholly accounted for by the psychiatric diagnoses we have

excluded. Further, the categorical nature of DSM-III-R psychiatric diagnoses makes this instrument insensitive to the continuum of psychiatric symptoms typically presented by these patients.

Since determining premorbid psychiatric status is based on retrospective self report of symptoms, we can never clearly establish its presence or absence without prospective studies. Therefore, as a next step, rather than continue to emphasize premorbid psychiatric status, it will be more fruitful to identify concurrent behavioral factors that may be contributing to or exacerbating this illness. In our present study we exclude individuals with a clear premorbid psychiatric history and document current psychiatric status among the remainder. Our emphasis is on identifying psychological concomitants of chemical sensitivity as well as standardized evaluation of the neuropsychological symptoms and odor sensitivity of these patients.

METHOD

Subjects:

The first question we have addressed is whether chemically sensitive patients can be identified according to the criteria proposed by Cullen (1987). That is, do patients exist who meet these criteria?

Chemically sensitive subjects were recruited from patients referred to our Environmental and Occupational Health Clinical Center. Over the past three years, we have evaluated 37 patients for chemical sensitivity. During this three year study period, twenty-three of these patients met the following criteria for chemical sensitivity (Cullen, 1987): 1) initial symptoms acquired in relation to an identifiable environmental exposure(s), 2) symptoms involve more than one organ system, 3) symptoms recur and abate in response to predictable stimuli, 4) symptoms are elicited by low-level exposures to chemicals of diverse structural classes, 5) no standard test of organ system function can explain symptoms. In addition, our subjects were not in litigation at the time of our evaluation and were not receiving treatment from a clinical ecologist. Fourteen of the 37 patients met some but not all of these criteria and are referred to as Mixed MCS Features. Six Mixed MCS Features patients could not report a clear onset for the development of chemical sensitivity. An additional four Mixed MCS Features were excluded because they did not report sensitivities to multiple substances, and four other Mixed MCS Features patients had other pre-existing conditions (i.e. psychiatric history with treatment).

Chemically sensitive subjects had no physical and/or psychiatric history or current diagnosis that could explain the development, breadth, and severity of their symptoms. This was determined by the self-report medical questionnaire routinely administered to all clinic patients as well as physical and laboratory examination. At that time, only a cursory overview of psychiatric history was included, i.e., history of psychiatric hospitalization or treatment by a mental health professional on an inpatient or outpatient basis. The exposures and substances that are reported to initiate and/or elicit symptoms are based solely on subjective historical information provided by the subjects.

Eighteen normal controls were recruited from our Internal Medicine Clinic. The medical records of these controls were screened for the following major illnesses: cardiovascular disease, uncontrolled hypertension, neurologic disorder, liver disease, kidney disease, serious gastrointestinal disease, pulmonary disease (asthma), symptoms in response to ongoing exposure to toxins, inpatient hospitalization for psychiatric disorders. Normal controls were also screened for chemical sensitivity as defined by the above criteria.

Table 1 shows the demographic characteristics of the chemically sensitive patients, chemically sensitive patients who met some but not all of the criteria, and normal control subjects. The MCS and normal controls were not significantly different in age, education, or current reading ability. Features of MCS subjects were similar to MCS subjects on age, education and reading ability. However, unlike MCS, the Mixed MCS Features group had no males.

Evaluation Measures:

Medical Evaluation

Each potential subject underwent a comprehensive medical examination by an occupational medicine

most consistent with the somatoform disorders of DSM-III-R. This result can be seen in the group profile of MCS patients on the MMPI-2 (Table 6). That is, MCS patients as a group present a profile that is consistent with conversion or somatization disorders.

In addition to the MMPI-2, the somatization interview of the Diagnostic Interview Survey for the DSM-III-R was used to determine the presence of these symptoms both before the development of MCS and currently. The results for MCS, and normals can be seen in Table 7. On the average, compared to normal controls, MCS subjects report a significantly greater number of unexplained somatic complaints, most of which they attribute to MCS. One of the criteria for somatization disorder is that the patient must have had at least one unexplained symptom before the age of 30. Forty-eight percent (11/23) of the MCS subjects had at least one symptom before the age of 30 as contrasted to normal controls (note that one MCS subject was 30 at the time of the research). Finally, 17% (4/23) MCS subjects qualified for a diagnosis of somatization disorder based on the number of symptoms reported. Two of those 4 MCS subjects did not have any unexplained symptoms before age 30. Therefore, technically 9% (2/23) of MCS subjects met all criteria for somatization disorder. Table 8 shows the specific somatization disorder symptoms reported by MCS and normal controls. Overall, MCS subjects report significantly more arm/leg and chest pain, blurred vision, trouble walking and weakness, dizziness, unusual spells, gastrointestinal, and respiratory symptoms than normal controls.

DISCUSSION

The results of our work, thus far, suggest that a subset of MCS patients can be selected to meet the criteria proposed by Cullen (1987). That is, approximately 2/3 of the patients referred for chemical sensitivity meet the criteria as proposed by Cullen. Further, the majority (83%) of the patients meeting these criteria do not have a premorbid psychiatric diagnosis as determined both by history and by self-report on a structured psychiatric interview. While only two of our patients meet the DSM-III-R criteria for somatization disorder (i.e., 13 symptoms with at least one symptom before the age of 30), as a group, they report numerous symptoms that are consistent with somatization disorder. Their MMPI-2 profiles are also consistent with those of conversion disorder or somatoform patients. That is, they have numerous health complaints with no apparent medical explanation to substantiate these complaints.

Due to the inherent biases in retrospective, self-report data, the question of psychiatric predisposition to chemical sensitivity can never be resolved without a prospective study. However, such a study will be difficult to undertake until we have more information about the prevalence of this problem. Our experience suggests that the prevalence of this disorder is relatively small in the population particularly when a more restrictive definition is used for case selection. Determining whether these patients have a higher rate of psychiatric disorder does not address the behavioral factors that may contribute to the symptoms experienced by these patients. For example, while MCS patients appear to be similar in their symptom profile to somatization disorder patients, what does this mean? As a diagnosis, somatization disorder is not well understood, and in fact, some studies suggest that this is often a misdiagnosed physical illness. For example, Mersky & Buhrich (1975) reported that 67% of patients diagnosed as conversion disorder were later found to have one of several physical illnesses that were initially difficult to identify.

Our approach to the study of MCS is multidisciplinary and incorporates both physical and psychological parameters to help explain our patients' responses to chemicals. In our experience, traditional psychiatric diagnoses and labels have not been particularly helpful in explaining the reactions of these patients nor in leading to effective treatment. Therefore, while we continue to document the rate of traditional psychiatric disorders among our patients, a more important aspect of the psychiatric portion of our ongoing research involves identification of relevant behavioral traits. A substantial literature has been developed regarding the behavioral factors that influence reporting of physical symptoms (e.g. Leventhal). For example, alexithymia refers to the focus on the somatic rather than the emotional component of arousal (Bagby et al., 1988). This construct may help explain a part of the reactions

that chemically sensitive patients have to chemicals. Similarly, physical symptoms may be amplified by a heightened sensitivity to physical stimuli in general (e.g. I am more sensitive to pain than others) (Barsky et al., 1988). Both of these behaviors are being assessed using standardized instruments in our ongoing work. Another aspect of this work also involves the response of these patients to odors. In 90% of our patients, odors are generally involved in their perception of reactions and exposures. Therefore, we are assessing our patients' ability to discriminate (UPSIT) (Doty et al., 1984) and to detect odors (threshold). In addition, during threshold testing, we will have patients discriminate their symptoms in response to odors typically regarded as olfactory vs. trigeminal (e.g. burning, tingling).

Another important issue in MCS research is the choice of an appropriate control group. MCS most closely resembles the somatoform disorders of DSM-IIR. Therefore, if MCS is a distinct diagnostic category, it is important to distinguish MCS from somatoform patients. In addition, other medically ill groups (e.g. asthmatics) also become symptomatic in the presence of chemicals that most of us tolerate. Since MCS patients often have respiratory symptoms, we have chosen asthmatics as a medically ill control group which has symptoms and reactions that overlap with those of MCS patients.

In summary, our work does not indicate that MCS fits perfectly into any existing psychiatric diagnostic category. While MCS resembles many aspects of somatization disorder, this offers little to explain the etiology or maintenance of this disorder nor the triggering by environmental stimuli.

TABLE 1: DEMOGRAPHICS OF SUBJECT GROUPS

	MCS (N=23) Mean(SD) Range	MCS Features (N=14) Mean (SD) Range	Normal Controls (N=18) Mean (SD) Range
Sex Ratio	M(4) F(19)	M(0) F(14)	M(4) F(14)
Age	43(9) 28-58	47(7) 35-59	45(10) 28-63
Education	15(3) 11-20	15(2) 12-19	16(2) 12-20
WRAT-R*	103(13) 82-122	104(11) 84-123	106(15) 82-126

* Wide Range Achievement Test- Reading Standard Score
No significant differences in age, education, WRAT-R

TABLE 2: SUMMARY OF INITIATING EVENTS

	N
Chemicals (Solvents, Paint, Spray Mount, Pesticides)	9
Carpet/Carpet Adhesive	7
Indoor Air	4
Medication Reaction/Denture Cleaner	2
Home Cleaning Products	1

TABLE 3: CURRENT REVIEW OF SYMPTOMS

Percent Reporting

	MCS (N=23)		Normal Controls (N=18)	
	%	N	%	N
RESPIRATORY	**83**	**19**	**61**	**11**
Shortness of Breath	74	17	17	3
GENITOURINARY	**78**	**18**	**33**	**6**
Frequent Urination	30	7	11	2
Loss of Sex Drive	30	7	1	1
MUSCULOSKELETAL	**87**	**20**	**61**	**11**
Back Pain	70	16	50	9
Muscle or Joint Pain	74	17	39	7
SKIN	**70**	**16**	**50**	**9**
Dry Skin	43	10	33	6
NERVOUS SYSTEM	**91**	**21**	**61**	**11**
Headaches	87	20	17	3
Dizziness	74	17	11	2
Unusual Fatigue	74	17	1	1
Unusual Weakness	61	14	1	1
GASTROINTESTINAL	**83**	**19**	**28**	**5**
Nausea or Vomiting	57	13	1	1
Abdominal Pain	43	10	12	2
CARDIOVASCULAR	**83**	**19**	**50**	**9**
Chest Pain	52	12	0	0

TABLE 4: SUBSTANCE QUESTIONNAIRE DATA

	N	Mean (SD)	Mode	Range
MCS	23	38(22)	31	9-85
MCS Features	14	78(29)	13	13-111
Normal Controls	18	12(14)	0	0-50

TABLE 5: STRUCTURED CLINICAL INTERVIEW*

	MCS Percent (Ratio)	Normal Control Percent (Ratio)	p
PREMORBID DIAGNOSIS:**			
Depression	13 (3/23)	11 (2/18)	ns
Anxiety Disorders	4 (1/23)	0	ns
Prescription Drug Abuse	0	0	ns
No Diagnosis	83 (19/23)	89 (16/18)	ns
CURRENT DIAGNOSIS:			
Depression	17 (4/23)	0	.08
Anxiety Disorders	0	0	ns
Prescription Drug Abuse	0	0	ns
No Diagnosis	83 (19/23)	100 (18/18)	.08

*Somatization section was excluded
**One subject in each group had more than one diagnosis

TABLE 6: MMPI-2 MEAN T SCORES

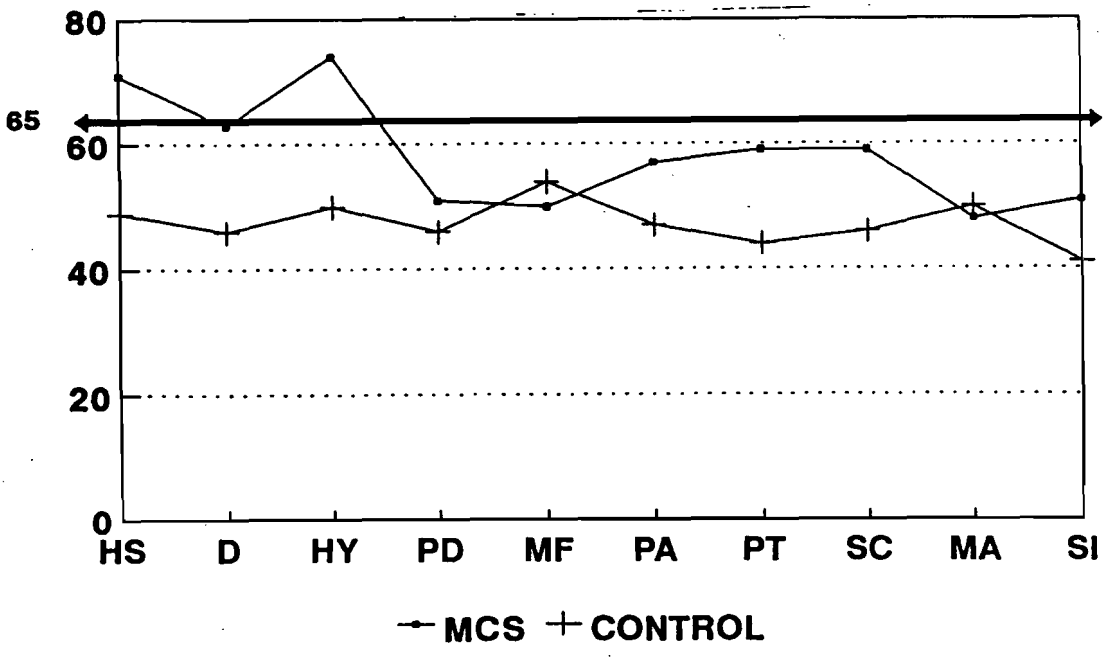


TABLE 7: DIAGNOSTIC INTERVIEW SCHEDULE

	Post-MCS* (N=22) Mean (SD) Range	Controls** (N=18) Mean (SD) Range
Symptoms with Medical Explanation	2 (2) 0-6	3 (3) 0-9
Symptoms with No Medical Explanation	6 (4) 0-16	1 (1) 0-56

* Four (18%) subjects had 13 or more somatization symptoms, 2 of the 4 had symptoms prior to age 30
**No subjects had 13 or more somatization symptoms, 5 (28%) had symptoms prior to age 30

TABLE 8: NIMH DIAGNOSTIC INTERVIEW SCHEDULE

Percent Unexplained Medical Symptoms

	MCS (N=23)		Normal Controls (N=18)		p*
	%	N	%	N	
PAIN					
Belly Pain	9	2	11	2	-
Back Pain	18	4	0	0	-
Joint Pain	32	7	11	2	-
Arm/Leg Pain	27	6	0	0	.02
Chest Pain	64	14	5	1	.0001
Pain Elsewhere	18	4	0	0	-
Headaches	50	11	11	2	.009
Painful Menses	32	7	11	2	-
Pain Urinating	9	2	0	0	-
Pain in Private Parts	9	2	0	0	-
NERVOUS SYSTEM					
Blurred Vision	36	8	0	0	.004
Lost Hearing	5	1	0	0	-
Trouble Walking	23	5	0	0	.04
Lost Feeling-Arms/Legs	23	5	0	0	.04
Paralyzed	9	2	0	0	-
Weakness	45	10	0	0	.0007
Lost Voice	18	4	0	0	-
Seizures	5	1	0	0	-
Fainting	18	4	0	0	-
Dizzy	50	11	17	3	.02
Amnesia	9	2	0	0	-
Unusual Spells	36	8	0	0	.004
GASTROINTESTINAL					
Vomiting	5	1	0	0	-
Nausea	45	10	0	0	.0007
Diarrhea	27	6	0	0	.01
Gas/Bloating	32	7	5	1	.04
Constipation	18	4	0	0	-
Foods Make Ill	5	1	5	1	-
RESPIRATORY/CARDIO VASCULAR					
Shortness of Breath	50	11	0	0	.0003
Palpitations	55	12	17	3	.01

*Fishers Exact Test

REFERENCES

Bagby, R.M., Taylor, G.J., Atkinson, L. Alexithymia: A Comparative Study of Three Self-Report Measures. J Psychosom Res 32:107-116, 1988.

Barsky et al. Psychosomatic Medicine 1988;50:510-519.

Black, E.W., Rathe, A., Goldstein, R. Environmental Illness - A Controlled Study of Twenty-six Subjects with 20th Century Diseases. JAMA 1990;264:3166-3170.

Brodsky, C.M. Psychological Factors Contributing to Somatoform Diseases Attributed to the Workplace. J Occup Med 1983;25:459-464.

Cheren, S. Psychosomatic Medicine. Connecticut: International Universities Press, Inc. 1989.

Cullen, M.R. The Worker with Multiple Chemical Sensitivities: An Overview. In: Cullen M, ed. Workers with Multiple Chemical Sensitivities. Philadelphia, PA: Hanley & Belfus Inc. 1987;655-662.

Doty, R.L. et al. Development of the University of Pennsylvania Smell Identification Test: A Standardized Microencapsulated Test of Olfactory Function. Physiol & Behav 1984;32:489-501.

Fiedler, N., Maccia, C., Kipen, H. Evaluation of Chemically Sensitive Patients. Journal of Occup Med 1992;34:529-538.

Hathaway, S.R., McKinley, J.C. Minnesota Multiphasic Personality Inventory Manual - Revised. New York: The Psychological Corporation, 1967.

Mersky and Buhrich, 1975.

Robins, L.N., Helzer, J.E. Diagnostic Interview Schedule (DIS) Version III-A. St. Louis, MO: Washington School of Medicine. 1985.

Shottenfeld, R. Workers with Multiple Chemical Sensitivities: A Psychiatric Approach to Diagnosis and Treatment. State Art Rev Occup Med. 1987;2:739-753.

Simon, G.E., Katon, W.J., Sparks, P.J. Allergic to Life: Psychological Factors in Environmental Illness. Am J Psychiatry 1990;147:901-906.

Spitzer, R.L., Williams, J.B.W., Gibbon, M. et al. User's Guide for the Structured Clinical Interview for DSM-III-R. Washington, DC: American Psychiatric Press, Inc. 1990.

DEPRESSION, SOMATIZATION AND CHRONIC FATIGUE SYNDROME:

LESSONS FOR THE STUDY OF MULTIPLE CHEMICAL SENSITIVITY.

Susan E. Abbey, M.D., F.R.C.P.(C)

Affiliation: Director, Psychosomatic Medicine Program
The Toronto Hospital
Assistant Professor, Department of Psychiatry
University of Toronto

Correspondence: Department of Psychiatry
8 EN-212
The Toronto Hospital
200 Elizabeth Street
Toronto, Ontario
M5G 2C4

Telephone: (416)340-4160
Fax: (416)340-4198

DEPRESSION, SOMATIZATION AND CHRONIC FATIGUE SYNDROME:

LESSONS FOR THE STUDY OF MULTIPLE CHEMICAL SENSITIVITY.

Chronic fatigue syndrome (CFS) is a recently described disorder which has come to prominence since the mid 1980's (Dubois et al 1984, Behan et al 1985, Jones et al 1985, Salit 1985, Straus et al 1985, Buchwald et al 1987, Straus 1988). CFS shows many similarities with multiple chemical sensitivity (MCS) in terms of the prominence of non-specific physical and psychological symptoms (Dubois et al 1984, Behan et al 1985, Jones et al 1985, Salit 1985, Straus et al 1985, Buchwald et al 1987, Straus 1988, Taerk et al 1987, Kruesi et al 1989, Wessely & Powell 1989, Hickie et al 1990, Gold et al 1990, Katon et al 1991b, Wood et al 1991), the absence of a "gold standard" for diagnosis (Holmes et al 1988), the prominence of emotional distress (Taerk et al 1987, Kruesi et al 1989, Wessely & Powell 1989, Hickie et al 1990, Gold et al 1990, Katon et al 1991b, Wood et al 1991) and ongoing debates as to the significance of the emotional and psychiatric symptoms associated with the disorder (Abbey & Garfinkel 1990, Abbey & Garfinkel 1991, Wessely 1990, Ray 1991, Katon & Walker 1993, Wessely 1993, Abbey 1993). The scientific study of CFS and MCS has been hampered by the fact that there is no single widely accepted test of physiological function or laboratory abnormality that can be shown to correlate with the symptoms and which defines the disorder. Thus, in the absence of specific objective and reproducible testing, it is difficult to determine "cases" and to differentiate "cases" from patients with other medical and psychiatric disorders which present with similar symptomatology. Despite these many problems, the psychiatric study of CFS has advanced over recent years. The purpose of this article is to delineate some of the lessons from the study of the psychiatric aspects of CFS which may be useful in the further study of the psychiatric aspects of MCS.

Chronic Fatigue Syndrome: The Birth of a New Diagnosis

Case definition criteria for CFS were proposed by Holmes et al (1988) (see Table 1). There has been considerable debate about the appropriateness of these criteria (Lloyd 1990, Sharpe 1991) and the usefulness of these criteria in delineating a homogenous sample of patients for study which allows comparability between study sites. The criteria were re-evaluated in a meeting sponsored by the United States National Institute of Health in 1991, and modifications have been proposed as shown in Table 1 (Schluederberg et al 1992). It is clear that a variety of patients meet case definition criteria for CFS. Katon and Russo (1992) have argued that the emphasis on multiple somatic symptoms biases the criteria to include patients with high levels of psychiatric morbidity. Interestingly, groups which have compared patients with chronic fatigue and chronic fatigue syndrome (Katon et al 1991b, Manu et al 1993) have reported that there are not substantial differences between these two groups of patients. Recent work has also suggested that amongst those suffering from CFS there is considerable heterogeneity with regards to initiating and maintaining factors in the development and perpetuation of the disorder.

Clinical and research work has documented that there a variety of patients who presently meet case definition criteria or have a clinical presentation compatible with CFS including patients with: chronic fatigue syndrome, primary undiagnosed or misdiagnosed medical illness, primary undiagnosed or misdiagnosed psychiatric illness, and a complex presentation with the combination of a viral or physical initiating event, psychiatric pathology and illness behaviour. It is likely, that similar subgroupings will be defined for patients presenting with MCS.

Psychiatric Symptomatology in CFS and MCS

When samples of patients carrying diagnoses of CFS and MCS are studied from the psychiatric viewpoint, it is possible to identify patients who meet the diagnostic criteria of the American Psychiatric Association Diagnostic and Statistical

Manual, Third Edition, Revised for either current or lifetime psychiatric disorders. The significance of these findings remains controversial (Abbey & Garfinkel 1990, Abbey & Garfinkel 1991, Wessely 1990, Ray 1991, Katon & Walker 1993, Wessely 1993, Abbey 1993) and will be discussed at greater length in this paper. The potential relationships between psychiatric symptomatology and chronic fatigue syndrome are outlined in table 2. The psychiatric findings in studies of chronic fatigue syndrome patients are summarized in table 3. The prevalence of psychiatric symptomatology in studies of patients with MCS or environmental hypersensitivity illness is shown in table 4. In reviewing these tables, it is important to realize that there is likely considerable variation between studies in the characteristics of patients sampled reflecting the previously discussed problems of case definition.

Lessons from the Psychiatric Study of Chronic Fatigue Syndrome

While psychiatric symptoms and emotional distress were described in the early case series reports of CFS (Dubois et al 1984, Behan et al 1985, Jones et al 1985, Salit IE 1985, Straus et al 1985, Buchwald et al 1987), systematic study of the psychiatric aspects of CFS did not begin until the work of Taerk et al (1987). Subsequent authors have studied the psychiatric symptoms and diagnoses in samples of patients with chronic fatigue and CFS (Kruesi et al 1989, Wessely & Powell 1989, Hickie et al 1990, Gold et al 1990, Katon et al 1991b, Wood et al 1991), personality and CFS (Millon et al 1989, Blakely et al 1991) and cognitive function in CFS patients (Altay et al 1990, Grafman et al 1991, DeLuca et al 1993, Grafman et al 1993). Recent attention has focused on the role of psychiatric treatment in terms of both cognitive-behavioural (Wessely et al 1989, Butler et al 1991, Wessely et al 1991) and psychopharmacological (Goodnick & Sandoval 1993, Abbey in press) components in the comprehensive rehabilitation of patients with chronic fatigue syndrome. The study of the psychiatric aspects of CFS has taught us a number of lessons which are summarized in table 5 and which are relevant for the development of comprehensive research into the nature of MCS.

(1) Primary psychiatric disorders can present with bodily symptoms.

Psychiatric disorders are characterized by disturbances in thinking (cognitive symptoms), feeling (affective symptoms) and bodily function (somatic symptoms). The relative importance of the different symptoms varies across patients, diagnoses and treatment settings. The lay understanding of psychiatric diagnoses primarily focuses on cognitive and affective symptoms but somatic symptoms are extremely common in all of the psychiatric diagnoses. The prominence of bodily symptoms within the psychiatric diagnoses can be seen by reviewing the diagnostic criteria for major depressive episode (MDE), panic disorder (PD) and somatization disorder (SD) which are summarized in table 6. The differential presentation of these psychiatric diagnoses in psychiatric settings compared with primary care and other medical settings has been commented on by a number of authors who have noted that the physical symptoms associated with psychiatric disorders are more commonly reported by patients seen in primary care and other medical settings than in psychiatric settings (Goldberg 1979, Goldberg 1984, Katon 1982a, 1982b, 1989). Somatic symptoms of psychiatric disorders have received less attention than the cognitive and affective symptoms of these disorders. Abbey and Garfinkel (1991) have discussed the reasons for the relative lack of attention to the somatic symptoms of depression and have noted that this reflects both the interests of research psychiatrists and the types of patients typically enrolled in research studies in academic tertiary care facilities. When attention is paid to somatic symptoms of depression it is found that there is a high prevalence of such symptoms (Mathew et al 1981, Wittenborn & Buhler 1979) and it has been noted that it is difficult to identify a cohort of patients who do not report somatic symptoms of depression (Kreitman et al 1965).

Numerous researchers have demonstrated that patients with psychiatric disorders or emotional distress which is subsyndromal have more medically unexplained symptoms than do patients without psychiatric disorders (Matthew et al 1981, Pennebaker 1982, Bridges & Goldberg 1985, Waxman et al 1985, Escobar et al 1987, Katon & Russo 1989). Similarly, it has been demonstrated that patients who are high utilizers of medical care and have a large number of medically unexplained

symptoms also have high rates of current and lifetime diagnoses of depression and anxiety disorders (Katon et al, 1990).

A wide range of physical symptoms were noted in the depressed patients studied by Wessely and colleagues (Wessely & Powell 1989, Powell et al 1990) as well as in the CFS patients. Our own preliminary data (Abbey, Garfinkel & Salit, unpublished) documents that greater than 40% of patients with major depressive episode report symptoms of fatigue, exhaustion, fatigue worse after physical and mental exertion, weakness, muscle aches, nausea, fever, sweats, lightheadedness, dizziness, sore throat, pain, odd sensations in the skin, change in appetite, and itching.

The relationship between physical symptoms and psychiatric disorders is a complex one. Somatization is the term which has been applied to the tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for these symptoms (Lipowski, 1988). There are three components to the process of somatization: the perceptual awareness of a symptom, the cognitive interpretation placed upon the symptom, and the behavioural outcome of medical help-seeking (Lipowski, 1988). There are a wide variety of explanations for somatization including genetic factors, childhood exposure to illness and social learning factors, the premium our society places on somatic diagnosis, and the physiological concomitants of psychiatric disorder. The related concept of somatic amplification refers to the fact that any physical symptom is the result of two components -- a peripheral sensation and then a cortical elaboration or "reactive component" which results in the amplification or minimization of the physical symptom (Barsky et al 1988). Somatic amplification may occur because of psychological reasons, sociocultural forces, situational reasons, and the objective in seeking medical care. These and a variety of other explanations have been postulated for the occurrence of physical symptoms in depressive disorders (Abbey & Garfinkel, 1991). Sharpe & Bass (1992) have described a range of physiological and psychological mechanisms associated with somatization. Amongst the physiological mechanisms are factors such as autonomic arousal, muscle tension, hyperventilation, vascular changes, alterations in cerebral information processing and evoked potentials and the secondary effects of sleep disturbance and inactivity. Psychological mechanisms implicated in somatization include mood disturbance, personality factors, beliefs, and perceptual factors. The relative contribution of each of these factors varies across individuals and it is likely that both physiological and psychological mechanisms interact in a given individual (Sharpe & Bass, 1992).

Some authors have suggested that the symptom complex in MCS may be mediated by psychological processes. Shusterman et al (1988) have described "behavioral sensitization to odorants", a mechanism by which irritant symptoms couple with fear of toxicity resulting in a panic attack and ultimately a conditioned response where irritant exposure leads to repeated panic attacks. Selner & Staudenmire (1986, 1993) have noted that the evaluation of illness related to environmental factors requires recognition of psychological mechanisms that can influence the expression and interpretation of symptoms. They have emphasized the concept of "learned sensitivity" which argues that conditioned responses which were classically thought to be limited to "stimulus-response pairing" should be enlarged to include conscious and automatic cognitively mediated processes such as expectations, beliefs and influences about causal relationships. They argue that an evaluation of stimuli, intermediary psychophysiological reactions and cognitive processes are important in truly understanding those factors which maintain multiple chemical sensitivity.

(2) Patients with a diagnosis of CFS may have misdiagnosed or undiagnosed primary psychiatric disorders.

Popular press coverage of CFS is replete with symptom lists. It is not unsurprising that individuals with primary psychiatric disturbance may either inaccurately label themselves as having CFS or be inaccurately diagnosed by their physician as having CFS based on the overlap of symptoms of psychiatric disturbance and CFS. The importance of recognizing this is that there are now highly effective treatments for many of the psychiatric disorders including major depression, panic disorder and generalized anxiety disorder. While the relationship between depression and CFS is a problematic one, and there is likely no one

relationship that is applicable to all patients (Abbey & Garfinkel, 1991), it is clear that there are patients who are diagnosed with CFS when in fact they have a primary psychiatric disorder (eg. major depression) and treatment of that disorder leads to a complete remission of their CFS symptoms (Abbey, in press).

(3) Psychiatric diagnoses remain highly stigmatized.

Kirmayer & Robbins (1991) have emphasized that psychiatric and psychosomatic disorders remain highly stigmatized in our society and have described somatization as a "sociomoral problem". They note that there is "an inescapable moral dimension" to psychosomatic diagnoses and that those disorders which are viewed as psychologically caused or mediated are viewed as under voluntary control and hence the patient may be viewed as "causing" their own illness. The cartesian dualism of "mind and body" is extended such that personal causation, responsibility and blame are attached to problems of psychological origin while problems seen as arising from the body are not "caused" by the patient. Powell et al (1990) have documented the potential benefits of a physical rather than a psychological attribution in a study of patients with CFS. The stigmatization of psychiatric disorders make it difficult both in terms of the research inquiry into the area and also developing effective treatment strategies for the emotional symptoms that are part of CFS. This appears to be true as well for MCS. Unfortunately, physicians are often not good at conveying to patients the way in which psychosocial stress, life events and psychiatric disorders may be translated into bodily symptoms through physiological mechanisms. Thus all too often the patient feels devalued and blamed. English (1991), a physician with CFS, notes "I have talked with scores of fellow patients who went to our profession for help, but who came away humiliated, angry and afraid. Their bodies told them they were physically ill, but the psychospeculation of their physicians was only frightening and infuriating -- not reassuring".

(4) The factors initiating CFS may be very different from the factors which maintain the ongoing disability.

It has been suggested that the factors important in initiating CFS may be very different from those factors which maintain the ongoing disability (Wessely et al 1989, Sharpe 1993) as has been described for the post-concussional syndrome (Lishman 1988). Wessely et al (1991) have argued that while an initial viral infection might produce fatigue and myalgia, inactivity and depression, later in the course of the illness the problem becomes a self-reinforcing cycle of responses in which fatigue and myalgia produce inactivity which in turn produces symptoms leading to avoidance which in turn produces more symptoms and results in loss of control and demoralization and ultimately depression which in itself is associated with fatigue and myalgia. This cycle may result in the maintenance or perpetuation of CFS long after the initial viral insult has disappeared (Wessely et al 1991). The "cyclical" view of the maintaining factors in CFS opens the possibility for treatment with interventions targeted to different phases of the cycle (Wessely et al 1991, Sharpe 1990). Cognitive-behavioural treatments which have been effective in the treatment of chronic pain (Benjamin 1989), rheumatoid arthritis (O'Leary et al 1988) and irritable bowel syndrome (Litt & Baker 1987). Psychotropic medications may be useful in the treatment of depression, anxiety and sleep disorders which accompany CFS and may also provide some symptom relief in patients without co-morbid mood or sleep disturbances (Abbey 1993). Simon (1992) and Haller (1993) have suggested a similar integrated treatment program for patients with MCS.

The importance of attributions to prognosis in the clinical course of patients with CFS has been emphasized by British researchers. Sharpe et al (1992) in a study of outcome of CFS patients assessed in an infectious disease clinic documented that a worse outcome was associated with the patient making an entirely physical attribution for their problems and membership in a patient advocacy group.

(5) The treatment of the psychiatric symptoms associated with CFS as the necessary first step in rehabilitation.

Recent attention has focused on the importance of taking a rehabilitation approach with patients with CFS. This is predicated on the hypothesis that the initiating factors for the syndrome may be very different from those factors which maintain

provocative although equivocal (Hickie et al 1990, Abbey & Garfinkel, 1991). There is evidence of alterations in a variety of immune parameters including lymphocyte number and function, and immunoglobulin and complement levels in some patients with major depression (Kronfol et al 1983, Schleifer et al 1984, Kronfol et al 1985, Kronfol et al 1986, Targum et al 1989, Cosyns et al 1989, Maes et al 1989, Schleifer et al 1989, Calabrese et al 1986, Murphy et al 1987, Darko et al 1988, Darko et al 1988b, Darko et al 1988c, Kronfol & House 1989, Maes et al 1992a & 1992b) although this has not been replicated by all studies (Schleifer et al 1985, Albrecht et al 1985, Altshuler et al 1989, Schleifer et al 1989, Maes et al 1989). Natural killer cell activity has been demonstrated to be decreased in patients with major depression (Nasrallah et al 1987, Irwin et al 1990, Kronfol et al 1989, Evans et al 1992). Studies of natural killer cell activity in individuals exposed to social stress (Dorian et al 1982, Locke et al 1984) and bereavement (Irwin et al 1987) have documented a decrease in activity which is correlated with the severity of depressive symptoms (Irwin et al 1987, Locke et al 1984). A variety of other abnormalities have been demonstrated. Abnormalities in hypothalamo-pituitary-adrenal axis have been postulated to underlie both depression and chronic fatigue syndrome and may be mediated by cytokines (Ur et al 1992). A wide variety of factors might account for the variability in these findings: patient demographic characteristics (eg. age and sex distribution), severity and duration of depressive episode, comorbid psychiatric disorders, neuroendocrine status, the use of other medications which interfere with immune functioning, the presence of other factors known to alter immune function such as weight loss, protein-calorie malnutrition, cigarette smoking, alcohol use, sleep deprivation, and technical differences in the protocols used to test parameters (Hickie et al 1990, Abbey & Garfinkel 1991, Stein et al 1991, Andreoli et al 1992, Calbrese et al 1987, Stein et al 1987, Altshuler et al 1989, Irwin et al 1990, Schleifer et al 1989). Studies are just beginning which include control groups of patients with major depression (Lloyd et al 1992).

Similarly, the interpretation of abnormal findings in studies of neuroimaging in CFS (Ichise et al 1992) have been complicated by the fact that there are abnormalities in PET and SPECT neuroimaging of a variety of psychiatric disorders (Morihisa 1987, Wu et al 1991).

The neuropsychological study of CFS is in its infancy. Peyser et al (1990) have reviewed the problems in conducting neuropsychological research in multiple sclerosis and their guidelines have some utility in the study of the neuropsychological aspects of CFS and MCS. Wessely (1993) has reviewed the initial neuropsychological studies of CFS which have been equivocal. Recent publications by DeLuca et al (1993) and Grafman et al (1993) have demonstrated some neuropsychological impairments. DeLuca et al (1993) reported on a study of CFS and multiple sclerosis patients demonstrating that CFS patients showed an impairment in a test of complex concentration. Grafman et al (1993) demonstrated some mild memory impairment on tasks requiring conceptually driven encoding and retrieval processes. Neither study included a group of depressed patients. Abbey and Garfinkel (1991) have emphasized the importance of including psychiatric controls given the possibility that depression may on its own be associated with neuropsychological abnormalities (Robbins et al 1992) and has already been noted there are high rates of depression in CFS samples. While there remains a debate as to the presence and severity of neuropsychological impairment in major depression, there is evidence of abnormalities in sustained concentration (Mayeux et al 1981), effortful encoding of memory (Squire et al 1984, Taylor et al 1986, Saint-Cyr et al 1988, Golinkoff & Sweeney 1989, Watts et al 1990), central executive memory functions (Channon et al 1993) retrieval of newly learned information and psychomotor speed (Mayeux et al 1981, Taylor et al 1986).

Comparison groups have also been useful in helping to more carefully delineate which components of the phenomenology of the disorder are specific to CFS and which aspects may be related to other processes. Wessley & Powell (1989) is the best study to date in comparing three groups of patients on measures of psychopathology, symptoms of fatigue and causal attribution. Patient groups included CFS, peripheral neuromuscular disease and psychiatric patients with a major depressive episode. Interestingly, the use of these three groups revealed that physical fatigue didn't differentiate between the groups while mental fatigue characterized the

patients with CFS, major depressive and those neuromuscular patients who had a co-morbid psychiatric diagnosis. Thus, the use of three groups allows for the beginning dissection of the characteristics of fatigue which are specific to CFS and those which are not. Causal attribution was found to vary between the groups despite similarities in their overall symptom patterns.

(9) Research studies must include a rigorous psychiatric evaluation so that the sample can be appropriately characterized and data can be stratified.

There has been considerable debate about what constitutes an adequate psychiatric evaluation in patients with CFS. There are problems in the psychiatric assessment of any patient with physical illness (Rodin et al, 1991) and specific problems in the psychiatric assessment of patients with CFS. The problem of how to assess somatic symptoms which may be attributable to either medical illness or psychiatric illness is a vexing one (Abbey et al 1990) and a variety of approaches have been used by different clinicians and researchers (Cohen-Cole & Stoudemire, 1987, Rodin et al, 1991). Cohen-Cole & Stoudemire (1987) have summarized the different approaches which have been used: the exclusion of somatic symptoms which may be attributable to either disorder, the inclusion of such symptoms and the substitution of somatic symptoms with additional cognitive and affective symptoms. Lustman et al (1986) have described the technique of analyzing the data so as to include and exclude the somatic symptoms and then compare the rates of psychiatric diagnosis. A similar approach has been used by some researchers studying CFS (Kruesi et al 1989, Wood et al 1991).

The psychiatric assessment of patients can be classified as categorical or dimensional. The intent of categorical assessment is to establish the prevalence of formal psychiatric diagnoses while the intent of dimensional assessment is to document the frequency or intensity of various psychiatric symptoms. While categorical and dimensional assessments may show some overlap, they are essentially different approaches with different methodologies. In categorical assessment, the goal is to ascertain whether a patient meets established diagnostic criteria for a given psychiatric diagnosis. At the present time, most North American researchers use the criteria of American Psychiatric Association Diagnostic and Statistical Manual, Third Edition, Revised (1987) although other diagnostic systems and criteria exist. In dimensional assessments, the goal is describe the intensity of either emotional distress in general or a particular psychiatric symptom such as depression or anxiety. Commonly used scales measuring both emotional distress and depressive severity have been reviewed by Thase (1991) and their applicability in medically ill patients has been reviewed by Rodin et al (1991). Measures which have been used by CFS researchers are summarized in table 7.

The psychiatric assessment of patients is complicated by a number of other issues including the retrospective nature of symptom reporting and temporal sequencing of symptoms. Problems related to attributions about symptoms and their etiology may reflect patient or subject concerns about psychiatric stigma which may lead to inaccurate reporting. The psychiatric assessor may be faced with the problem of what to do when there is a mismatch between subjective and objective measures. It has been agreed that in assessing CFS patients, it is important that there be an interviewer who is skilled in eliciting psychopathology, and that multiple measures be used reflecting both categorical and dimensional measures of a wide range of psychopathology. It is clear that it is important to specify the rationale for analysis and to consider the psychiatric symptoms within the pattern of CFS symptoms. All of the above concerns seem to be applicable to the psychiatric assessment of patients with MCS.

Conclusions

The relationship between psychiatric disorders and disorders such as CFS and MCS remains poorly understood and in need of rigorous study. It is clear however that this is an important area to pursue for the knowledge that will be gained both with regards to CFS and MCS and psychiatric disorders. The need for careful clinical assessment of patients presenting with self or physician conferred labels of CFS and MCS must be underlined as there are effective treatments now available for depression and anxiety which may accompany these disorders or which may be the primary diagnoses. The treatment of the psychiatric symptomatology

accompanying CFS and MCS offers sufferers a better quality of life. Well-designed, carefully controlled studies of the psychiatric aspects of these two disorders are urgently needed.

TABLE 1: CASE DEFINITION CRITERIA FOR CHRONIC FATIGUE SYNDROME (HOLMES ET AL, 1988)

Both major criteria and either ≥ 6 symptomatic criteria plus ≥ 2 physical criteria or ≥ 8 symptomatic criteria must be present to fulfil the case definition.

Major Criteria

1. Persistent or relapsing fatigue or easy fatiguability that does not resolve with bed rest and is severe enough to reduce average daily activity by ≥ 50%
2. Other chronic clinical conditions have been satisfactorily excluded[1]

Minor Criteria

Symptomatic or historical criteria: persistent or recurring symptoms lasting ≥ 6 months:

1. Mild fever (37.5 C - 38.6 C oral) or chills
2. Sore throat
3. Lymph node pain in anterior or posterior cervical or axillary chains
4. Unexplained generalized muscle weakness
5. Muscle discomfort, myalgia
6. Prolonged (≥ 24 h) generalized fatigue following previously tolerable levels of exercise
7. New, generalized headaches
8. Migratory noninflammatory arthralgia
9. Neuropsychological symptoms: photophobia; transient visual scotoma; forgetfulness; excessive irritability; confusion; difficulty thinking; inability to concentrate; depression
10. Sleep disturbance
11. Patient's description of initial onset of symptoms as acute or subacute

Physical criteria: documented by a physician on at least two occasions, at least 1 mo apart:

1. Low grade fever (37.6 C - 38.6 C oral or 37.8 C - 38.8 C rectal)
2. Nonexudative pharyngitis
3. Palpable or tender anterior or posterior cervical or axillary lymph nodes (< 2 cm in diameter)

[1]See Schluederberg et al (1992) for clarifications re. exclusions & inclusions

TABLE 2: POTENTIAL RELATIONSHIPS BETWEEN PSYCHIATRIC SYMPTOMATOLOGY AND CHRONIC FATIGUE SYNDROME

1. Primary psychiatric symptomatology is misdiagnosed as chronic fatigue syndrome.

2. Psychiatric symptomatology occurs as the result of chronic fatigue syndrome on the basis of either:

   (a) an organic mood syndrome (eg. neurotropic virus, influence of cytokines or lymphokines on the central nervous system, etc.)

   (b) a reaction to having a poorly understood, controversial diagnosis which is extremely disabling and for which there is no clear treatment.

3. Chronic fatigue syndrome and psychiatric symptomatology may be covariate phenomena.

4. Psychiatric diagnosis may be inaccurately made when symptoms which are due to chronic fatigue syndrome are artefactually counted towards a psychiatric diagnosis.

(Abbey & Garfinkel, 1991)

TABLE 3: PREVALENCE OF CURRENT PSYCHIATRIC DIAGNOSES IN STUDIES OF PATIENTS WITH CFS

	Sample Size	Diagnostic Criteria	Comparison Groups	Common Current Axis I Psychiatric Diagnoses
Taerk et al (1987)	24	clinical	healthy controls	NR; lifetime prevalence of major depression and dysthymia 67%; panic disorder 13%
Wessely & Powell (1989)	47	clinical	neuromuscular disease, major depression	47% major depression; generalized anxiety disorder; 15% somatization disorder
Kruesi et al (1989)	28	CDC	no	46% major depression; 7% somatization disorder
Gold et al (1990)	26	23% CDC retrospective	healthy controls	42% major depression
Hickie et al (1990)	48	Lloyd et al 1988b	nonendogenous depression	21% major depression; 3% panic disorder; 3% somatization disorder
Katon et al (1991)	98	19% CDC	rheumatoid arthritis	15.3% major depression; 11% dysthymia; 28.5% anxiety disorder , 46 % somatization disorder
Wood et al (1991)	34	clinical	muscle disease	23.5% depressive neurosis; 12% phobic neurosis; 6% generalized anxiety neurosis; 6% somatization disorder

CDC = Case definition criteria (Holmes et al, 1988)
NR = not reported

TABLE 4: PREVALENCE OF PSYCHIATRIC SYMPTOMATOLOGY IN STUDIES OF PATIENTS WITH MCS OR ENVIRONMENTAL ILLNESS

	Sample Size	Referral Source	Diagnostic Criteria	Comparison Groups	Current Axis I Psychiatric Diagnoses
Brodsky (1983)	8	disability claimants	clinical	no	63% major depression
Schottenfield & Cullen (1985)	21	occupational medicine clinic	medically unexplained symptoms	no	14% posttraumatic stress disorder; 33% atypical posttraumatic stress disorder; 52% somatoform disorder
Stewart & Raskin (1985)	18	physicians & lawyers	clinical	no	17% major depression or dysthymia; 22% anxiety disorder; 17% psychotic disorder; 39% somatoform disorder
Terr (1989)	90	disability claimants	clinical	no	11% major depression; 13% anxiety disorder; 19% somatoform disorder - all diagnoses made by prior consultants with no formal psychiatric assessment as part of study
Black et al (1990,1993)	26	volunteers solicited through advertisements, clinics, support groups	clinical	yes - normal controls from psychiatric studies	39% major depression; 43% anxiety disorder; 17% somatoform disorder
Simon et al (1990)	13	disability claimants	clinical	other disability claimants	92% major depression or anxiety disorder
Sparks et al (1990)	53	disability claimants	clinical	no	60% major depression; 26% anxiety disorder; 6% somatoform disorder
Fiedler et al (1992)	11	occupational medicine	Cullen (1987) criteria for MCS	no	36% major depression
Simon et al (1993)	41	allergist	modified Cullen (1987) criteria for MCS	chronic musculo-skeletal disease	29% major depression; 24% anxiety disorder; 26% somatoform disorder

TABLE 5: THE STUDY OF THE PSYCHIATRIC ASPECTS OF CFS HAS TAUGHT US

1. Primary psychiatric disorders can present with bodily symptoms.

2. Patients with a diagnosis of CFS may have misdiagnosed or undiagnosed primary psychiatric disorders.

3. Psychiatric disorders remain highly stigmatized.

4. The factors which initiate chronic fatigue syndrome may be very different from the factors which maintain the disability associated with the syndrome.

5. The treatment of the psychiatric symptoms associated with CFS is the necessary first step in rehabilitation.

6. The importance of social and cultural factors in illness experience.

7. Case definition criteria which incorporate a large number of nonspecific or functional somatic symptoms increase the likelihood of patients with somatization disorder being misdiagnosed as having the syndrome.

8. Research studies should incorporate comparison sample(s) of patients with primary psychiatric disorders if the issue under study includes abnormalities in immune functioning, brain imaging or neuropsychological functioning.

9. Research studies must include a rigorous psychiatric evaluation so that the sample can be appropriately characterized and that data can be stratified.

TABLE 6: DSM-III-R DIAGNOSTIC CRITERIA[1] FOR PSYCHIATRIC DISORDERS COMMONLY DIAGNOSED IN PATIENTS WITH CHRONIC FATIGUE SYNDROME AND MULTIPLE CHEMICAL SENSITIVITY

Panic Disorder (with or without agoraphobia)

A. Panic attacks which on at least one occasion have been unexpected and not triggered by situations in which the person was the focus of others' attention.

B. Four attacks within four weeks or one or more attacks followed by at least a month of persistent fear of having another attack.

C. At least 4 of the following symptoms developed during at least one of the attacks:
- shortness of breath (dyspnea) or smothering sensations
- dizziness, unsteady feelings, or faintness
- palpitations or accelerated heart rate (tachycardia)
- trembling or shaking
- sweating
- choking
- nausea or abdominal distress
- depersonalization or derealization
- numbness or tingling sensations (paresthesias)
- flushes (hot flashes) or chills
- chest pain or discomfort
- fear of dying
- fear of going crazy or of doing something uncontrolled

D. During at least some of the attacks, at least four of the C symptoms developed suddenly and increased in intensity within ten minutes of the beginning of the first C symptom noticed in the attack.

E. It cannot be established that an organic factor initiated and maintained the disturbance, eg. amphetamine or caffeine intoxication, hyperthyroidism

Generalized Anxiety Disorder

A. Unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances for a period of six months or longer

B. If another Axis I disorder is present, the focus of the anxiety and worry in A is unrelated to it, eg. the anxiety or worry is not about having a panic attack (as in Panic Disorder).

C. Does not occur only during the course of a mood disorder or a psychotic disorder and if there is another disorder present, the anxiety or worry is not related (eg. fear of being embarrassed in public with social phobia, being contaminated with obsessive-compulsive disorder, gaining weight with anorexia nervosa)

D. At least 6 of the following 18 symptoms:

Autonomic Hyperactivity
Shortness of breath
Palpitations, tachycardia
Sweating, cold clammy hands
Dry mouth
Dizziness or lightheadedness
Nausea, diarrhea, abdominal distress
Flushes (hot flashes) or chills
Frequent urination
Trouble swallowing/lump in throat

Motor Tension
Trembling, twitching
Muscle tension, aches
Restlessness
Easy fatigability

Vigilance & Scanning
Feeling keyed up/on edge
Exaggerated startle
Difficulty concentrating
Trouble falling/staying asleep
Irritability

E. It cannot be established that an organic factor initiated and maintained the disturbance, eg. hyperthyroidism, caffeine intoxication

Major Depressive Episode

A. At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure.

(1) depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day, as indicated either by subjective account or observation by others
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time)
(3) significant weight loss or weight gain when not dieting (eg. more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. (1) It cannot be established that an organic factor initiated and maintained the disturbance
(2) The disturbance is not a normal reaction to the death of a loved one

C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms

Somatization Disorder

A. A history of many physical complaints or a belief that one is sickly, beginning before the age of 30 and

persisting for several years.

B. At least 13 of the following 35 symptoms. To count a symptom as significant, the following criteria must be met:

(1) no organic pathology or pathophysiologic mechanism to account for the symptom or, when there is related organic pathology, the complaint or resulting social or occupational impairment is grossly in excess of what would be expected from the physical findings
(2) has not occurred only during a panic attack
(3) has caused the person to take medicine (other than over-the-counter pain medication), see a doctor, or alter life-style

Symptom list:

Gastrointestinal symptoms:
(1) vomiting (other than during pregnancy)
(2) abdominal pain (other than when menstruating)
(3) nausea (other than motional sickness)
(4) bloating (gassy)
(5) diarrhea
(6) intolerance of (gets sick from) several different foods

Pain symptoms:
(7) pain in extremities
(8) back pain
(9) joint pain
(10) pain during urination
(11) other pain (excluding headaches)

Cardiopulmonary symptoms:
(12) shortness of breath when not exerting oneself
(13) palpitations
(14) chest pain
(15) dizziness

Conversion or pseudoneurologic symptoms:
(16) amnesia
(17) difficulty swallowing
(18) loss of voice

Conversion or pseudoneurologic symptoms (cont'd):
(19) deafness
(20) double vision
(21) blurred vision
(22) blindness
(23) fainting or loss of consciousness
(24) seizure or convulsion
(25) trouble walking
(26) paralysis or muscle weakness
(27) urinary retention or difficulty urinating

Sexual symptoms for the major part of the person's life after opportunities for sexual activity:
(28) burning sensation in sexual organs or rectum (other than during intercourse)
(29) sexual indifference
(30) pain during intercourse
(31) impotence

Female reproductive symptoms judged by the person to occur more frequently or severely than in most women:
(32) painful menstruation
(33) irregular menstrual periods
(34) excessive menstrual bleeding
(35) vomiting throughout pregnancy

[1]Adapted from American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association, 1987 (with permission).

TABLE 7: MEASURES USED IN THE CATEGORICAL & DIMENSIONAL ASSESSMENT OF PSYCHOPATHOLOGY IN CFS PATIENTS

I. Categorical Assessment

Instrument	Study
SADS - Schedule for Affective Disorder and Schizophrenia (Spitzer & Endicott 1977)	Wessely & Powell, 1989
DIS - Diagnostic Interview Schedule (Robins et al, 1981)	Taerk et al, 1987 Gold et al, 1990 Kruesi et al, 1989
SCID - Structured Clinical Interview for DSM-III-R (Spitzer et al, 1985)	Hickie et al, 1990
PSE - Present State Examination (Wing et al, 1974)	Wood et al, 1991

II. Dimensional assessment

A. Nonspecific Measures of Psychological Morbidity or Distress

Instrument		Study
General Health Questionnaire (Goldberg 1972)	12 item 28 item 30 item	Wessely & Powell 1989 Blakely et al, 1991 Hickie et al, 1990
Symptom Checklist-90 (Derogatis, 1977)		Gold et al, 1990

B. Self-report Measures of Depressive Symptomatology

Instrument	Study
Beck Depression Inventory - 13 item (Beck & Beck, 1972)	Blakely et al, 1991
HADS - Hospital Anxiety & Depression Scale (Zigmond & Snaith 1983)	Wessely & Powell 1989 Wood et al 1991
Zung Self-Rating Depression Scale (Zung 1965)	Hickie et al, 1990

C. Observer Rated Measures of Depressive Symptomatology

Instrument	Study
Hamilton Rating Scale for Depression (Hamilton, 1960)	Hickie et al, 1990
Newcastle Depression Scale (Carney et al, 1965)	Hickie et al, 1990

D. Self-report Measures of Somatic Symptomatology, Hypochondriasis & Illness Behaviour

Instrument	Study
Somatic Discomfort Questionnaire (Wittenborn & Buhler 1979)	Wessely & Powell,1989
Illness Behaviour Questionnaire (Pilowsky & Spence, 1983)	Hickie et al, 1990

REFERENCES

Abbey SE, Toner BB, Garfinkel PE, Kennedy SH, Kaplan AS. Self-report symptoms that predict major depression in patients with prominent physical symptoms. Int J Psychiatry in Medicine, 1990; 20:247-258

Abbey SE. Somatization, illness attribution and the sociocultural psychiatry of chronic fatigue syndrome. In GR Bock, J Whelan (eds) Chronic Fatigue Syndrome (Ciba Foundation Symposium 173). Chichester: Wiley, 1993a, p 238-261

Abbey S. Psychopharmacology and chronic fatigue syndrome. In S. Straus (ed). Chronic Fatigue Syndrome. New York: Marcel Dekker, Inc., 1993b, in press

Albrecht J, Helderman JH, Schlesser MA, Rush AJ. A controlled study of cellular immune function in affective disorders before and during somatic therapy. Psychiatry Res 1985; 15:185-93

Altay HT, Toner BB, Brooker H, Abbey SE, Salit IE, Garfinkel PE. The neuropsychological dimensions of postinfectious neuromyasthenia: a preliminary report. Int J Psychiatry Med 1990; 20: 141-9

Altshuler LL, Plaeger-Marshall S, Richeimer S, Daniels M, Baxter LR. Lymphocyte function in major depression. Acta Psychiatr Scand 1989; 80:132-6

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association, 1987

Andreoli A, Keller SE, Rabaeus M, Zaugg L, Garrone G, Taban C. Immunity, major depression and panic disorder comorbidity. Biol Psychiatry 1992; 31:896-908

Barsky AJ, Goodson JD, Lane RS, et al. The amplification of somatic symptoms. Psychosom Med 1988; 50:510-519

Beck AT, Beck RW. Screening depressed patients in family practice. A rapid technique. Postgrad Med 1972; 52:81-85

Behan PO, Behan WMH, Bell EJ. The postviral fatigue syndrome-an analysis of the findings in 50 cases. J Infect 1985; 10:211-22

Benjamin S. Psychological treatment of chronic pain: a selective review. J Psychosom Res 1989; 33:121-131

Black DW, Rathe A, Rise B, Goldstein, MSW. Environmental Illness. A controlled study of 26 subjects with '20th Century Disease'. JAMA 1990; 264:3166-70

Black DW, Rathe A, Goldstein RB. Measures of distress in 26 "environmentally ill" subjects. Psychosomatics 1993; 34:131-138

Blakely AA, Howard RC, Sosich RM, Murdoch JC, Menkes DB, Spears GFS. Psychiatric symptoms, personality and ways of coping in chronic fatigue syndrome. Psychol Med 1991; 21:347-362

Bridges KW, Goldberg DP. Somatic presentation of DSM-III psychiatric disorder in primary care. J Psychosom Res 1985; 29:563-569

Brodsky CM. "Allergic to everything": a medical subculture. Psychosomatics 1983; 24:731-742

Buchwald D, Sullivan JL, Komaroff AL. Frequency of chronic active Epstein-Barr virus infection in a

general medical practice. JAMA 1987; 257:2303-7

Butler S, Chalder T, Ron M, Wessely S. Cognitive behaviour therapy in chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 1991; 54:153-158

Calabrese JR, Kling MA, Gold PW. Alterations in immunocompetence during stress, bereavement, and depression: focus on neuroendocrine regulation. Am J Psychiatry 1987; 144:1123-34

Calabrese JR, Skwerer, Barna B, Gulledge AD, Valenzuela R, Butkus A, Subichin S, Krupp NE. Depression, immunocompetence, and prostaglandins of the E series. Psychiatry Res 1986; 17:41-47

Caligiuri M, Murray C, Buchwald D, Levine H, Cheney P, Peterson D, Komaroff AL, Ritz J. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. J Immuno 1987; 139:3306-3313

Channon S, Baker JE, Robertson MM. Working memory in clinical depression: an experimental study. Psychol Med 1993; 23:87-91

Chao CC, Gallagher M, Phair J, Peterson PK. Serum neopterin and interleukin-6 levels in chronic fatigue syndrome. J Infect Dis 1990; 162:1412-1413

Carney MWP, Roth M, Garside RF. The diagnosis of depressive symptoms and the prediction of ECT response. Br J Psychiatry 1965; 111:659-674

Cheney PR, Dorman SE, Bell DS. Interleukin-2 and the chronic fatigue syndrome. Ann Intern Med 1989; 110:321

Cohen-Cole SA, Stoudemire A. Major depression and physical illness: special considerations in diagnosis and biologic treatment. Psychiatric Clin N Am 1987; 10:1-17

Cosyns P, Maes M, Vandewoude M, Stevens WJ, DeClerck LS, Schotte C. Impaired mitogen-induced lymphocyte responses and the hypothalamic-pituitary-adrenal axis in depressive disorders. J Affective Disord 1989;16:41-8

Cullen MR. The worker with multiple chemical sensitivities: an overview. In M Cullen (ed) Workers with Multiple Chemical Sensitivities. Philadelphia: Hanley & Belfus Inc. 1987, p 655-662

Darko DR, Lucas AH, Gillin JC, Risch SC, Golshan S, Hamburger RN, Silverman MB, Janowsky DS. Cellular immunity and the hypothalamic-pituitary axis in major affective disorder: a preliminary study. Psych Res 1988; 25:1-9

Darko DR, Gillin JC, Risch SC, Bulloch K, Golshan S, Tasevska Z, Hamburger RN. Immune cells and the hypothalamic-pituitary axis in major depression. Psych Res 1988b; 25:173-179

Darko DR, Rose J, Gillin GC, Colshan S, Baird SM. Neutrophilia and lymphopenia in major mood disorders. Psych Res 1988c; 25:243-251

DeLuca J, Johnson SK, Natelson BH. Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. Arch Neurol 1993; 50:301-304

Derogatis LR. SCL-R-90 Scoring Manual I: Scoring, Administration and Procedures. Baltimore, Md: Johns Hopkins University School of Medicine Clinical Psychometrics Unit, 1977

Dorian B, Garfinkel P, Brown G, Shore A, Gladman D, Keystone E. Aberrations in lymphocyte subpopulations and function during psychological stress. Clin Exp Immunol 1982; 50:132-138

Dubois RE, Seeley JK, Brus I, Sakamoto K, Ballow M, Harada S, Bechtold TA, Pearson G., Purtilo DT. Chronic mononucleosis syndrome. South Med J 1984; 77:1376-82

English TL. Skeptical of skeptics. JAMA 1991; 265:964

Escobar JI, Burnham MA, Karno M, Forsythe A, Golding JM. Somatization in the community. Arch Gen Psychiatry 1987; 44:713-718

Evans DL, Folds JD, Petitto JM, Golden RN, Pedersen CA, Corrigan M, Gilmore JH, Silva SG, Quade D, Ozer H. Circulating natural killer cell phenotypes in men and women with major depression: relation to cytotoxic activity and severity of depression. Arch Gen Psychiatry 1992;

49:388-395

Ewan C, Lowy E, Reid J. "Falling out of culture": the effects of repetition strain injury on sufferers' roles and identity. Sociol Health Illness 1991; 13:168-192

Fiedler N, Maccia C, Kipen H. Evaluation of chemically sensitive patients. J Occup Med 1992; 34:529-538

Gold D, Bowden R, Sixbey J, Riggs R, Katon WJ, Ashley R, Obrigewitch R, Corey L. Chronic fatigue: a prospective clinical and virologic study. JAMA 1990; 264:48-53

Goldberg D. The Detection of Psychiatric Illness by Questionnaire. London: Oxford University Press, 1972

Goldberg D. Detection and assessment of emotional disorders in a primary-care setting. Int J Ment Health 1979; 8:30-48

Goldberg D. The recognition of psychiatric illness by non-psychiatrists. Aust N Z J Psychiatry 1984; 18:128-33

Goodnick PJ. Bupropion in chronic fatigue syndrome. (letter) Am J Psychiatry 1990; 147:1091.

Goodnick PJ, Sandoval R, Brickman AL, Klimas NG. Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. Biol Psychiatry 1992; 32:834-838

Goodnick PJ, Sandoval R. Psychotropic treatment of chronic fatigue syndrome and related disorders. J Clin Psychiatry 1993; 54: 13-20

Golinkoff M, Sweeney JA. Cognitive impairments in depression. J Affect Dis 1989; 17:105-112

Gracious B, Wisner KL. Nortriptyline in chronic fatigue syndrome: a double blind, placebo-controlled single case study. Biol Psychiatry 1991; 30:405-408.

Grafman J, Johnson R, Scheffers M. Cognitive and mood-state changes in patients with chronic fatigue syndrome. Rev Infect Dis 1991; 13(Suppl 1):S45-52

Grafman J, Schwartz V, Dale JK, Scheffers M, Houser C, Straus SE. Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 1993; 56:684-689

Grufferman S. Issues and problems in the conduct of epidemiologic research on chronic fatigue syndrome. Rev Infect Dis 1991; 13(Suppl1):S60-67

Gupta S, Vayuvegula B. A comprehensive immunological analysis in chronic fatigue syndrome Scand J Immunol 1991; 33:319-327

Haller E. Successful management of patients with "multiple chemical sensitivities" on an inpatient psychiatric unit. J Clin Psychiatry 1993; 54:196-199

Hamilton M. A rating scale for depression. J Neurol, Neurosurg, Psychiatry 1960; 23:56-62

Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, Jones JF, Dubois RE, Cunningham-Rundles C, Pawha S, Tosato G, Zegans LS, Purtilo DT, Brown N, Schooley RT, Brus I. Chronic fatigue syndrome: a working case definition. Ann Intern Med 1988; 108:387-9

Hickie I, Lloyd A, Wakefield D, Parker G. The psychiatric status of patients with the chronic fatigue syndrome. Br J Psychiatry 1990; 156:534-40

Hickie I, Silove D, Hickie C, Wakefield D, Lloyd A. Is there immune dysfunction in depressive disorders? Psychol Med 1990; 20:755-761

Ichise M, Salit IE, Abbey SE, Chung DG, Gray B, Kirsh JC, Freedman M. Assessment of regional cerebral perfusion by $^{99}Tc^{m}$-HMPAO SPECT in chronic fatigue syndrome. Nucl Med Comm 1992; 13:767-772

Irwin M, Daniels M, Bloom ET, Smith TL, Weiner H. Life events, depressive symptoms, and immune function. Am J Psychiatry 1987; 144:437-41

Irwin M, Patterson T, Smith TL, Caldwell C, Brown SA, Gillin JC, Grant I. Reduction of immune function in life stress and depression. Biol Psychiatry 1990; 27:22-30

Jones JF, Ray CG, Minnich LL, Hicks MJ, Kibler

R, Lucas DO. Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: elevated anti-early antigen antibodies. Ann Intern Med 1985;102:1-7

Katon W, Kleinman A, Rosen G. Depression and somatization: a review. Part 1. Am J Med 1982; 72:127-35

Katon W. Depression: somatic symptoms and medical disorders in primary care. Compr Psychiatry 1982; 23:274-287

Katon W, Russo J. Somatic symptoms and depression. J Fam Pract 1989; 29:65-69

Katon W, von Korff M, Lin E, Lipscomb P, Russo J, Wagner E, Polk E. Distressed high utilizers of medical care: DSM-III-R diagnoses and treatment needs. Gen Hosp Psychiatry 1990; 12:355-362

Katon W, Lin R, von Korff M, Russo J, Lipscomb P, Bush T. Somatization: a spectrum of severity. Am J Psychiatry 1991a; 148:34-40

Katon WJ, Buchwald DS, Simon GE, Russo JE, Mease PJ. Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis. J Gen Intern Med 1991b; 6:277-285

Katon W, Walker EA. The relationship of chronic fatigue to psychiatric illness in community, primary care and tertiary care samples. In GR Bock, J Whelan (eds) Chronic Fatigue Syndrome (Ciba Foundation Symposium 173). Chichester: Wiley, 1993, p 193-211

Katon W, Russo J. Chronic fatigue syndrome criteria: a critique of the requirement for multiple physical complaints. Arch Intern Med 1992; 152:1604-1609

Kiecolt-Glaser JK, Glaser R. Stress and the immune system: human studies. In A Tasman, MB Riba (eds) American Psychiatric Press Review of Psychiatry, Vol 11. Washington DC: American Psychiatric Press, 1992, p 169-180

Kirmayer LJ, Robbins JM. Conclusion: prospects for research and clinical practice. In LJ Kirmayer, JM Robbins (eds) Current Concepts of Somatization: Research and Clinical Perspectives. Washington: American Psychiatric Press, Inc., 1991, p. 201-225

Kleinman A. Social Origins of Distress and Disease: Depression, Neurasthenia, and Pain in Modern China. New Haven: Yale University Press, 1986

Kleinman A. The Illness Narratives: Suffering, Healing and the Human Condition. New York: Basic Books, 1988

Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. J Clin Microbiol 1990; 28:1403-1410

Klimas NG, Morgan R, van Riel F, Fletcher MA. Observations regarding use of an antidepressant, fluoxetine, in chronic fatigue syndrome. In: PJ Goodnick, NG Klimas (eds) Chronic Fatigue and Related Immune Deficiency Syndromes. Washington: American Psychiatric Press, Inc., 1993, pp 95-108

Komaroff AL, Geiger AM, Wormsely S. IgG subclass deficiencies in chronic fatigue syndrome. Lancet 1988; i:1288-1289

Kreitman N, Sainsbury P, Pearce K, Costain WR. Hypochondriasis and depression in out-patients at a general hospital. Br J Psychiatry 1965; 111:607-15

Kronfol Z, House JD. Lymphocyte mitogenesis, immunoglobulin and complement levels in depressed patients and normal controls. Acta Psychiatr Scand 1989; 80:142-147

Kronfol Z, House JD, Silva J Jr, Greden J, Carroll BJ. Depression, urinary free cortisol excretion and lymphocyte function. Br J Psychiatry 1986; 148:70-3

Kronfol Z, Nair M, Goodson J, Goel K, Kaskett R, Schwartz S. Natural killer cell activity in depressive illness: preliminary report. Biol Psychiatry 1989; 26:753-6

Kronfol Z, Nasrallah HA, Chapman S, House JD. Depression, cortisol metabolism and lymphocytopenia. J Affective Disord 1985; 9:169-73

Kronfol Z, Silva J Jr, Greden J, Dembinski S, Gardner R, Carroll B. Impaired lymphocyte function in depressive illness. Life Sci 1983; 33:241 -7

Kruesi MJP, Dale J, Straus SE. Psychiatric diagnoses in patients who have chronic fatigue syndrome. J Clin Psychiatry 1989; 50:53-6

Landay AL, Jessop C, Lennette ET, Levy JA. Chronic fatigue syndrome: clinical condition associated with immune activation. Lancet 1991; 338:707-712

Lever AML, Lewis DM, Bannister BA, Fry M, Berry N. Interferon production in postviral fatigue syndrome. Lancet 1988; ii:101

Lipowski ZJ. Somatization: the concept and its clinical application. Am J Psychiatry 1988; 145:1358-1368

Lishman WA Physiogenesis and psychogenesis in the post-concussional syndrome. Br J Psychiatry 1988; 153:460-469

Litt MD, Baker LH. Cognitive-behavioral interventions for irritable bowel syndrome. J Clin Gastroenterol 1987; 2:208-211

Lloyd A, Hann DA, Wakefield D. Interferon and myalgic encephalomyelitis. Lancet 1988a; i: 471

Lloyd AR, Hales JP, Gandevia SC. Muscle strength, endurance and recovery in the post-infection fatigue syndrome. J Neurol Neurosurg Psychiatry 1988b; 51:1316-1322

Lloyd AR, Wakefield D, Boughton CR, Dwyer JM. Immunological abnormalities in the chronic fatigue syndrome. Med J Aust 1989; 151:122-124

Lloyd AR. Muscle versus brain: chronic fatigue syndrome: report from the recent international conferences on chronic fatigue syndrome in Los Angeles, USA and Cambridge, England

Lloyd A, Hickie I, Brockman A, Dwyer J, Wakefield D. Cytokine levels in serum and cerebrospinal fluid in patients with chronic fatigue syndrome and control subjects. J Infect Dis 1991; 164:1023-1024

Lloyd A, Hickie I, Hickie C, Dwyer J, Wakefield D. Cell-mediated immunity in patients with chronic fatigue syndrome, healthy control subjects and patients with major depression. Clin Exp Immunol 1992; 87:76-79

Locke SE, Kraus L, Leserman J, Hurst MW, Heisel JS, Williams RM. Life change stress, psychiatric symptoms, and natural killer cell activity. Psychosom Med 1984; 46:441-53

Lustman PJ, Harper GW, Griffith LS, Clouse RE. Use of the Diagnostic Interview Schedule in patients with diabetes mellitus. J Nerv Ment Dis 1986; 174:743-746

Lynch S, Seth R, Montgomery S. Antidepressant therapy in the chronic fatigue syndrome. Br J Gen Pract 1991; 41:339-342.

Maes M, Bosmans E, Suy E, Minner B, Raus J. Immune cell parameters in severely depressed patients: negative findings. J Affect Dis 1989; 17:121-128

Maes M, Bosmans E, Suy E, Minner B, Raus J. Impaired lymphocyte stimulation by mitogens in severely depressed patients: a complex interface with HPA-axis hyperfunction, noradrenergic activity and the ageing process. Br J Psychiatry 1989; 155:793-8

Maes M, Stevens WJ, DeClerck LS, Bridts CH, Peeters D, Schotte C, Cosyns P. A significantly increased number and percentage of B cells in depressed subjects: results of flow cytometric measurements. J Affect Dis 1992; 24:127-134

Maes M, van der Planken M, Stevens WJ, Peeters D, DeClerck LS, Bridts CH, Schotte C, Cosyns P. Leukocytosis, monocytosis and neutrophilia: hallmarks of severe depression. J Psychiat Res 1992b; 26:125-134

Manu P, Lane TJ, Matthews DA. Chronic fatigue and chronic fatigue syndrome: clinical epidemiology and aetiological classification. In GR Bock, J Whelan (eds) Chronic Fatigue Syndrome (Ciba Foundation Symposium 173). Chichester: Wiley, 1993, p 23-42

Mathew RJ, Weinman ML, Mirabi M. Physical

symptoms of depression. Br J Psychiatry 1981; 139:293-6

Mayeux R, Stern Y, Rosen J, Leventhal J. Depression, intellectual impairment and Parkinson disease. Neurology 1981; 31:645-50

Miller AH, Stein M. The immune system and depression. In A Tasman, MB Riba (eds) American Psychiatric Press Review of Psychiatry, Vol 11. Washington DC: American Psychiatric Press, 1992, pg. 181-201

Millon C, Salvato F, Blaney N, Morgan R, Mantero-Atienza E, Klimas N, Fletcher MA. A psychological assessment of chronic fatigue syndrome/chronic Epstein-Barr virus patients. Psychol Health 1989; 3:131-141

Morihisa JM. Functional brain imaging techniques. In RE Hales, AJ Frances (eds) American Psychiatric Association Annual Review Volume 6. Washington: American Psychiatric Association Inc. 1987, p 300-325

Morrison LJA, Behan WHM, Behan PO. Changes in natural killer cell phenotype in patients with post-viral fatigue syndrome. Clin Exp Immunol 1991; 83:441-446

Murphy D, Gardner R, Greden JF, Carroll BJ. Lymphocyte numbers in endogenous depression. Psychol Med 1987; 17:381-385

Nasrallah HA, Balla ZK, Kronfol Z, Chapman SM. Natural killer cell activity in major depression. In: Kurstak E, Lipowski ZJ, Morozov PV, eds. Viruses, immunity and mental disorders. New York: Plenum, 1987:369-72

O'Leary A, Shoor S, Lorig K, Holman HR. A cognitive-behavioural treatment for rheumatoid arthritis. Health Psychol 1988; 7:527-544

Pennebaker JW. The psychology of physical symptoms. New York: Springer-Verlag NY Inc., 1982

Peyser JM, Rao SM, LaRocca NG, Kaplan E. Guideline for neuropsychological research in multiple sclerosis. Arch Neurol 1990; 47:94-97

Pilowsky I, Spence ND. Manual for the Illness Behaviour Questionnaire (IBQ) (2nd edition). Adelaide: University of Adelaide, 1983

Powell R, Dolan R, Wessely S. Attributions and self-esteem in depression and chronic fatigue syndromes. J Psychosom Res 1990; 34:665-673

Prieto J, Subira ML, Castilla A, Serrano M. Naloxone-reversible monocyte dysfunction in patients with chronic fatigue syndrome. Scand J Immunol 1989; 30:13-20

Ray C. Chronic fatigue syndrome and depression: conceptual and methodological ambiguities. Psychol Med 1991; 21:1-9

Rest KM. Advancing the understanding of multiple chemical sensitivity (MCS): overview and recommendations from an AOEC workshop. In KM Rest (ed) Advancing the Understanding of Multiple Chemical Sensitivity: Proceedings of the Association of Occupational and Environmental Clinics (AOEC) Workshop on Chemical Sensitivity. Princeton: Princeton Scientific Publishing Co., Inc. 1992 pp 1-13

Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule. Arch Gen Psychiatry 1981a; 38:371-380

Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics and validity. Arch Gen Psychiatry 1981; 38:381-389

Robbins T, Joyce E, Sahakian B. Neuropsychology and imaging. In: E Paykel (ed) Handbook of Affective Disorders. Edinburgh: Churchill Livingstone, 1992, p 289-308

Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. Brain 1988; 111:941-59

Salit IE, Sporadic postinfectious neuromyasthenia. Can Med Assoc J 1985; 133:659-63

Schleifer SJ, Keller SE, Bond RN, Cohen J, Stein M. Major depressive disorder and immunity: role of age, sex, severity, and hospitalization. Arch Gen

Psychiatry 1989; 46:81-87

Schleifer SJ, Keller SE, Meyerson AT, Raskin MJ, Davis KL, Stein M. Lymphocyte function in major depressive disorder. Arch Gen Psychiatry 1984; 41:484-6

Schleifer SJ, Keller SE, Siris SG, Davis KL, Stein M. Depression and immunity: lymphocyte function in ambulatory depressed patients, hospitalized schizophrenic patients, and patients hospitalized for herniorrhaphy. Arch Gen Psychiatry 1985; 42:129-33

Schluederberg A, Straus SE, Peterson P, Blumenthal S, Komaroff AL, Spring SB, Landay A, Buchwald D. Chronic fatigue syndrome research: definition and medical outcome assessment. Ann Int Med 1992; 117:325-331

Schottenfeld RS, Cullen MR. Occupation-induced posttraumatic stress disorders. Am J Psychiatry 1985; 142:198-202

Selner JC, Staudenmayer H. Neuropsychophysiologic observations in patients presenting with environmental illness. In KM Rest (ed) Advancing the Understanding of Multiple Chemical Sensitivity: Proceedings of the Association of Occupational and Environmental Clinics (AOEC) Workshop on Chemical Sensitivity. Princeton: Princeton Scientific Publishing Co., Inc. 1992 p 1-13,145-155

Sharpe M. Chronic fatigue syndrome: can the psychiatrist help? In K Hawton, P Cowen (eds) Dilemmas and Difficulties in the Management of Psychiatric Patients. New York: Oxford University Press, 1990, p. 231-240

Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, Edwards RHT, Hawton KEH, Lambert HP, Lane RJM, McDonald EM, Mowbray JF, Pearson DJ, Peto TEA, Preedy VR, Smith AP, Smith DG, Taylor DJ, Tyrell DAJ, Wessely S, White P. A report - chronic fatigue syndrome: guidelines for research. J Roy Soc Med 1991; 84:118-121

Sharpe MC, Bass C. 1992 Pathophysiological mechanisms in somatization. Int Rev Psychiatry 1992; 4:81-97

Sharpe M, Hawton K, Seagroatt V, Pasvol G. Follow up of patients presenting with fatigue to an infectious disease clinic. Br Med J 1992; 305:147-152

Sharpe M. Non-pharmacological approaches to treatment. In GR Bock, J Whelan (eds) Chronic Fatigue Syndrome (Ciba Foundation Symposium 173). Chichester: Wiley, 1993, p 298-317

Shusterman D, Balmes J, Cone J. Behavioral sensitization to irritants/odorants after acute exposures. J Occup Med 1988; 30:565-567

Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. Am J Psychiatry 1990; 147:901-906

Simon GE. Psychiatric treatments in multiple chemical sensitivity. In KM Rest (ed) Advancing the Understanding of Multiple Chemical Sensitivity: Proceedings of the Association of Occupational and Environmental Clinics (AOEC) Workshop on Chemical Sensitivity. Princeton: Princeton Scientific Publishing Co., Inc. 1992 pp 67-72

Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. Immunologic, psychological and neuropsychological factors in multiple chemical sensitivity: a controlled study. Ann Int Med 1992; 119:97-103

Sparks PJ, Simon GE, Katon WJ, Altman LC, Ayars GH, Johnson RL. An outbreak of illness among aerospace workers. West J Med 1990; 153:28-33

Spitzer R, Endicott J. Schedule for Affective Disorders and Schizophrenia. New York: New York State Psychiatric Institute, 1977

Spitzer RL, Williams JBW, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992; 49:624-629

Squire LR, Cohen NJ, Zouzounis JA. Preserved memory in retrograde amnesia: sparing of a recently acquired skill. Neuropsychologia 1984;22:145-52

Stein M, Miller AH, Trestman RL. Depression, the immune system, and health and illness. Arch Gen

Psychiatry 1991; 48:171-177

Stein M, Schleifer SJ, Keller SE. Psychoimmunology in clinical psychiatry. In: Hales RE, Frances AJ, eds. Psychiatry update. Vol.6. Washington, DC: American Psychiatric Press, 1987:210-34

Stewart DE, Raskin J. Psychiatric assessment of patients with "20th-century disease" ("total allergy syndrome"). Can J Med 1985; 133:1001-1006

Stewart DE. The changing faces of somatization. Psychosomatics 1990; 31:153-158

Straus SE, Tosato G, Armstrong G, Lawley T, Preble OT, Henle W, Davey R, Pearson G, Epstein J, Brus I, Blaese RM. Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. Ann Intern Med 1985; 102:7-16

Straus SE. The chronic mononucleosis syndrome. J Infect Dis 1988; 157:405-12

Straus SE, Dale JK, Peter JB, Dinarello CA. Circulating lymphokine levels in the chronic fatigue syndrome. J Infect Dis 1989; 160:1085-1086

Straus SE, Fritz S, Dale JK, Gould B, Strober W. Lymphocyte phenotype and function in the chronic fatigue syndrome. J Clin Immunol 1993; 13:30-40

Subira ML, Castilla A, Civeira MP, Prieto J. Deficient display of CD3 on lymphocytes of patients with chronic fatigue syndrome. J Infect Dis 1989; 160:165-166

Taerk GS, Toner BB, Salt lE, Garfinkel PE, Ozersky S. Depression in patients with neuromyasthenia (benign myalgic encephalomyelitis). Int J Psychiatry Med 1987; 17:49-56

Targum SD, Marshall LE, Fischman P, Martin D. Lymphocyte subpopulations in depressed elderly women. Biol Psychiatry 1989; 26:581-9

Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. Brain 1986; 109:845-83

Taylor AE, Saint-Cyr JA, Lang AE, Kenny FT. Parkinson's disease and depression. A critical reevaluation. Brain 1986; 109:279-92

Terr AI. Clinical ecology in the workplace. J Occup Med 1989; 31:257-261

Thase ME. Assessment of depression in patients with chronic fatigue syndrome. Rev Infect Dis 1991; 13 (Suppl 1):S114-118

Ur E, White PD, Grossman A. Hypothesis: cytokines may be activated to cause depressive illness and chronic fatigue syndrome. Eur Arch Psychiatry Clin Neurosci 1992; 241:371-322

Ware NC. Suffering and the social construction of illness: the delegitimation of illness experience in chronic fatigue syndrome. Med Anthropol Q 1992; 6:347-361

Watts FN, Dalgleish T, Bourke P, Healy D. Memory deficit in clinical depression: processing resources and the structure of materials. Psychol Med 1990; 20:345-349

Wessely S, Powell R. Fatigue syndromes: a comparison of chronic "post-viral" fatigue with neuromuscular and affective disorders. J Neurol Neurosurg Psychiatry 1989; 52:940-8

Wessely S, David AS, Butler S, Chalder T. Management of chronic (post-viral) fatigue syndrome. J R Coll Gen Pract 1989; 39:26-29

Wessely S. Old wine in new bottles: neurasthenia and 'ME'. Psychol Med 1990; 20:35-53

Wessely S, Butler S, Chalder T, David A. The cognitive behavioural management of the post-viral fatigue syndrome. In R Jenkins, J Mowbray (eds) Post-viral Fatigue Syndrome. Chichester: Wiley 1991, p.305-334

Wessely S. The neuropsychiatry of chronic fatigue syndrome. In GR Bock, J Whelan (eds) Chronic Fatigue Syndrome (Ciba Foundation Symposium 173). Chichester: Wiley, 1993, p 212-237

Wing JK, Cooper JE, Sartorius N. The Measurement and Classification of Psychiatric Symptoms. London: Cambridge University Press,

1974

Wittenborn JR, Buhler R. Somatic discomforts among depressed women. Arch Gen Psychiatry 1979; 36:465-71

Wood GC, Bentall RP, Gopfert M, Edwards RHT. A comparative psychiatric assessment of patients with chronic fatigue syndrome and muscle disease. Psychol Med 1991; 21:619-628

Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. Biol Psychiatry 1991; 29:1181-1199

Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. Acta Psychiatry Scanda 1983; 67:361-70

Zung WWK A self-rating depression scale. Arch Gen Psychiatry 1965; 12:63-70

MULTIPLE CHEMICAL SENSITIVITY: MYTH OR REALITY

Arthur Leznoff, MD, FRCP(C) *
Associate Professor of Medicine
University of Toronto

*From the Divisions of Occupational Health and Clinical Immunology; Department of Medicine, St. Michael's Hospital, Toronto; and Faculty of Medicine, University of Toronto.

Corresponding Address: 38 Shuter Street, #215,
Toronto, Ontario MSB 1A6.
(416) 864-5855.

Key Words: Hyperventilation, Multiple Chemical Sensitivity, Environmental Sensitivity

ABSTRACT

This study attempted to identify pathophysiological mechanisms underlying the development of symptoms in some patients with multiple chemical sensitivity syndrome (MCS).

Fifteen patients whose symptom complex included breathlessness and light headedness were tested for evidence that exposure to their trigger chemicals affected pulmonary function or blood gases. In ten of these, challenge with a "domestic quantity" of an identified trigger resulted in observed profound hyperventilation which was corroborated by a dramatic fall in blood carbon dioxide and rise in oxygen. There was no evidence of upper or lower airway disease. The challenge produced no symptoms in the other five patients and there was no change in blood gases. This suggests that some of the symptoms of "chemical sensitivity" are a consequence of an anxiety reaction produced by the perception that the "chemicals" are offensive (resulting in hyperventilation) rather than by a direct toxic or reflex mechanism. Where there was no hyperventilation there were no symptoms.

In a second group of five (out of ten) patients who presented with throat related symptoms (choking, cough, dysphonia, "swollen glands"), challenge with the identified chemical produced no visible changes in the throat or larynx using fiberoptic laryngoscopy and no change in recorded phonograms. This negative finding occurred despite the patient's claim that the specific trigger caused dysphonia and throat swelling. We again concluded that symptoms were likely due to psychological rather than organic mechanisms.

In summary, challenge of MCS patients with identified trigger "chemicals" yielded evidence that suggests that this is a psychological disorder. We call it "CHEMOPHOBIA".

We have assessed thirty-five patients who fulfill the criteria for the existence of the problem of multiple chemical sensitivity (MCS) (1). On exposure they suffered a characteristic reproducible pattern of symptoms which is fairly constant for a given individual but which could vary among sufferers. There were few, if any, objective findings on physical examination, and common laboratory tests were normal. The trigger chemicals were multiple and were distributed among many chemical families including organic, inorganic, synthetic and biological (2). The concentrations which induced symptoms were "domestic concentrations" well tolerated by normals and many times below toxic thresholds. One characteristic of some of the chemicals typically identified is that they are often organic solvents, containing no reactive chemical groups, and therefore extremely unlikely to act as immunological haptens. Finally, the symptoms characteristically occur within minutes of exposure and gradually subside when exposure is terminated leaving no residual demonstrable pathology.

The symptoms described by the patients are similar to those often seen in patients with multiple, atypical, non IgE mediated food sensitivities (3). When such patients are tested with a double-blind placebo controlled food challenge, the patients react similarly to the challenge food and to the placebo proving that the putative sensitivities are illusory (3), and probably psychosomatic (4). In contradistinction to the above it is not possible to study whether MCS patients have "real" sensitivity using such double-blind challenges since many of these patients claim to react to all chemicals and since it is often impossible to disguise scents such as formaldehyde and cigarette smoke.

During the first few years of studying such patients it became obvious that the common methods of study yielded little information. All tests for organ dysfunction were negative. Although some patients complained of cough or choking and others of breathlessness, there was no objective evidence of respiratory disease. Many had received common inhalant and ingestant allergy tests which were irrelevant and often misleading. Many had seen practitioners of alternative medicine who administered "hocus pocus" testing such as sublingual, kinesthic or electrodiagnostic tests from which unfortunate conclusions were drawn. Many had seen psychiatrists or psychologists who did interviews and psychological screening tests and had various opinions. What was not done was the obvious - to challenge the patient with an identified trigger chemical to observe the consequences, and to measure something.

We proposed to investigate a sample of MCS patients by challenging them with various products in an open experiment to determine the pathophysiological mechanisms by which the perception of the stimuli leads to their symptoms. The procedures and measurements made were guided by the symptoms

described by the patients.

MATERIALS AND METHODS

Patients claiming to suffer from MCS were referred by Workers' Compensation Board, disability insurance carriers or for consultation concerning the possible allergic basis of their symptoms. Thirty-five patients were seen. In these patients we identified two major symptom complexes. While not mutually exclusive and though there were some symptoms common to both groups, the patterns were distinct. Both groups of symptoms have been reported in other studies (1,2).

Pattern A: Exposure induces headache, malaise, light headedness, impaired mentation, depersonalization, inco-ordination, breathlessness, weakness, parasthesias, sweating and palpitations.

Pattern B: The major symptoms relate to neck and throat. Patients complain of "tightness" in the throat, a sensation of swelling in the throat or neck (which is not confirmed objectively) and a feeling that neck "glands" are swollen (not confirmed objectively). They also complain of choking, hoarseness, cough and loss of voice. Symptoms which are common to both groups include a sense of impaired mentation and fatigue.

Fifteen of twenty-five patients with Type A symptoms consented to the challenge with one or more of the stimuli reported to induce their symptoms. Five of ten patients with Type B symptoms consented to challenge. The patients were asked to list common domestic "chemicals" which reliably and consistently produce the most dramatic symptoms. From this list we chose, for a given individual, an appropriate standard domestic product (i.e. perfume, cigarette smoke, hair spray, detergent) in standard concentrations with which to test the patient. For example, a perfumed hair spray might be aimed eighteen inches above the patient's head for twenty seconds or a volunteer would smoke a cigarette in the same room as the patient.

Clinical observations on the patients and appropriate measurements were designed depending on the patients' symptom complex. Where Type B symptoms were predominant fiberoptic laryngoscopy without local anaesthetic, and phonograms were obtained. Then the challenge was performed while the laryngoscope was in place, continuing for a minimum of ten minutes. Phonograms were performed during and after challenge exposure. Where Type A symptom complex was reported challenges were accompanied by measurement of respiratory parameters including flow volume curves, arterial, venous, or end tidal pCO_2 and pO_2 before and after the challenge.

All patients had previously been examined and had normal laboratory tests for complete blood count, erythrocyte sedimentation rate, serum glucose, creatinine, alkaline phosphatase, aspartate aminotransferase, urinalysis as well as normal pulmonary function tests and chest x-rays.

RESULTS

Two patterns of results and observations were observed. In ten of fifteen patients with Type A symptoms the challenge experiment quickly reproduced the symptoms described by the patients within two to fifteen minutes and often in dramatic fashion. All hyperventilated markedly (Table 1). In each of these patients there was no change in the flow volume curve demonstrating that asthma or stridor was not present, but there was a dramatic fall in pCO_2 with a rise in $p0_2$ (Table 2). This is consistent with the observed hyperventilation which is expected to produce exactly the same symptoms as described by the patients (5,6). All patients recovered in fifteen to ninety minutes.

In five of the Type A patients the above challenge experiments did not reproduce the symptoms anticipated by the patient and none of these showed changed in pCO_2 or $p0_2$.

The results of five challenges (in five of ten patients with Type B symptoms) are noted in Table 3. Essentially, nothing happened despite the fact that each patient had identified the challenge substance (in lower doses than used in the experiment) as a definite and reproducible trigger. There was no edema, no swelling, no vocal cord dysfunction no erythema and no change in the phonogram. One patient who had blamed her hoarseness on "chemicals" had multiple small vocal cord polyps. Her "chemical sensitivity" disappeared when these polyps were removed.

DISCUSSION

How do we interpret the above results? In the ten cases with observed and confirmed hyperventilation we have a very good explanation for the symptom complex

(Type A). The perception of the putative insult or trigger results in an acute panic or phobic reaction (6,7) with ensuing rapid and deep breathing in the absence of respiratory disease. The fall in pCO_2 predictably produces exactly the symptoms experienced by the patient (6,7). There was also clinical evidence of sympathetic and adrenergic stimulation with pallor, sweating, tremulousness and rise in cardiac rate, another expected component of a panic reaction (8). Removal of the trigger resulted in the expected improvement. This pattern is exactly the same as might occur in a patient with fear of heights at the top of the CN Tower or in a patient with agoraphobia in a crowded supermarket (10,11). For many reasons it is more acceptable to blame the symptoms on the smells rather than on the agora.

In the other patients tested, even though the experiment challenged the patients with a greater and more prolonged stimulus than they described as typically triggering their "sensitivity reactions", no symptoms were produced and no pathology was observed. The only conclusion to be drawn in these cases is that there are different factors involved in the genesis of the patients' symptoms which are distinct from the so-called chemical insults.

It has been suggested by proponents of the concept that MCS is an organic disease that subtle immune disorders are present in some patients. IgE mediated allergic responses have never been demonstrated to other than a few of the broad variety of "chemicals", and other immune reactions do not provoke immediate responses. Indeed there is no known organic mechanism by which the minute quantities of trigger odours or other stimuli can by themselves induce any immediate pathophysiologic abnormality other than by psychologically induced conditioned responses (7). The argument has been advanced that some speculative olfactory-limbic neuroreflexes or neurotransmitter abnormalities are involved (11) but a relationship to low dose chemical odours has not been convincingly demonstrated. Furthermore, patients such as cases 5 and 6 experienced the same symptoms from "the radiation exposure" secondary to proximity to a television screen or electric power lines where there is no olfactory stimulus. Other patients including our cases 5 and 8 develop identical symptoms from the ingestion of odourless foods such as sugar (3) and, in patient 10, tactile sensations in the hands produced by soft powder such as flour and baking soda constituted the trigger stimuli. Thus, the logical explanation is a psychologically mediated conditioned response with hyperventilation inducing the symptoms in the patients described (12). In other patients with Type B symptoms, other conditioned responses such as globus hystericus may occur.

It should be noted that patients who hyperventilate for reasons of anxiety or panic or phobic attacks do not achieve renal compensation by excretion of bicarbonate since they do not hyperventilate during sleep (5). Thus, during the daytime they consistently tend to be in respiratory alkalosis which is potentiated upon the perception of the stimulus which increases the respiratory rate and depth (5).

In summary we recognize there is a group of patients who have a distressing problem which is associated with low dose smells and chemicals. In none of these patients have we been able to demonstrate organic disease. In half of them we have shown physiological evidence of a panic or phobic reaction with marked hyperventilation to the degree that is expected to produce the symptoms described. Our conclusion is that MCS is not an organic disease but an emotional disorder in the family of panic attacks and phobias. We call it chemophobia.

REFERENCES

1. Cullen MR. The worker with multiple chemical sensitivities: An overview. In Cullen M. (ed). Workers with multiple chemical sensitivities-Occupation Medicine: State of the Art Reviews. Philadelphia: Hanley & Belfres Inc. 1987:2 (4) 633-661.

2. Mooser SB. The epidemiology of multiple chemical sensitivities. Occupational Medicine, State of the Art Reviews, 1987;2:663-668.

3. Parker SL, Leznoff A, Sussman GL, Tarlo S, Krondl M. Characteristics of patients with food-related complaints. J Allergy Clin Immunol 1990;86:503-511.

4. Parker SL, Garner DM, Leznoff A, Sussman GL, Tarlo S, Krondyl M. Psychological characteristics of patients with reported adverse reactions to foods. International J of Eating Disorders 1991;10:433-439.

5. Bass C, Gardner WN. Respiratory and psychiatric abnormalities in chronic symptomatic hyperventilation. Br Med J 1985; 290: 1387-90

6. Magarian GJ. Hyperventilation syndromes: infrequently recognized common expressions of anxiety and stress. Medicine (Baltimore) 1982;61:219-236.

7. Klein DF. Anxiety reconceptualized. Compr Psychiatry 1980; 21:411-427.

8. Diagnostic and Statistical Manual of Mental Disorders 3rd Ed Revised (DSM-III R) Washington DC. Am Psychiatric Assoc 1987;235-245.

9. Lelliott P, Marks I, McNamee G, Tobena A. Onset of panic disorder with agoraphobia. Arch Gen Psychiatry 1989;46:1000-1005.

10. Giarssen B, VanVeenendaal W, Bloemink R. Agoraphobia and the hyperventilation syndrome. Behav Res Ther 1983;21:643-9.

11. Brandwejn J, Koszyeki D, Meterissian G. Cholycystokinin-tetrapeptide induces panic attacks in patients with panic disorder. Can J Psychiatry 1990;35:83-85.

12. Regier DA, Narrow WE, Rae DS. The epidemiology of anxiety disorders: The epidemiologic catchment area (ECA) experience. J Psychiat Res 1990;24:(Supp 2) 3-14.

Table I Type A -Symptomatic Response to Challenge Substances

Case #	Sex, Age	Challenge Substance	Symptoms Before	Symptoms After
1	F42	Latex Paint	Anxiety	Triad * + Sweating
2	F39	Lab Smell	Headache	Triad + Weakness
3	M57	Hair Spray	Normal	Triad + Panic
4	M35	Asphalt Fumes**	Normal	Triad + Panic
5	F49	Disinfectant**	Anxiety	Triad + Tachycardia
6	M53	Liquid Bleach	Anxiety	Triad + Panic
7	F29	Acetone	Normal	Triad + Tremor
8	F37	Hair Spray	Normal	Triad + Crying
9	F44	Disinfectant	Normal	Triad + Weakness
10	F49	Flour, Tactile	Normal	Triad + Tremor

*Triad = Breathlessness without wheezing, light-headedness, confusion and incoordination.
** Challenge occurred inadvertently immediately prior to testing

Table II Blood Gases and ph in patients challenged with scents

Sample Source	Case #	pCO_2		pO_2		pH	
		Pre-Challenge	Post Challenge	Pre-Challenge	Post Challenge	Pre-Challenge	Post Challenge
Venous Blood	1	40	36	31	41	7.40	7.42
	2	32	29	41	51	7.42	7.48
	3	44	39	30	45	7.39	7.44
Arterial Blood	4*	-*	18	-	124	-	7.52
	5**	-**	20	-	92	-	7.57
End Tidal CO_2	6	22	13	98	-	7.49	-
	7	38	22	-	-	-	-
Oximeter	8	39	32	98	100	-	-
	9	37	29	97	104	-	-
	10	30	20	94	98	-	-

*Patient reacted to asphalt smell outside of hospital. Was hyperventilating on entering lab.
**Patient reacted to smell of sterilizing solution on entering lab, therefore no prechallenge measurements were made

Table III Effect of "Chemical" Challenge on Laryngoscopy

Patient #	Age/Sex	Challenge Chemical	Laryngoscopy		After Phonogram
			Before	After	
1	F27	perfume	normal	normal	normal
2	F46	NH_4 Detergent	normal	normal	normal
3	F34	cigarette smoke	normal	normal	normal
4	F29	hair spray	normal	normal	normal
5*	F22	nil	polyps	polyps	unchanged

*This patient had no chemical sensitivity after polyps were removed.

*CHEMICAL SENSITIVITY AND LOW-LEVEL EXPOSURES: SCIENTIFIC AND POLICY CONSIDERATIONS***[1]

N. A. ASHFORD* AND C. S. MILLER

Massachusetts Institute of Technology, Centre for Technology, Policy and Industrial Development, 77 Massachusetts Avenue E40-239, Cambridge, MA 01239, United States of America

ABSTRACT

Chemical sensitivity has become an increasingly important concern of those involved with indoor air quality. The nature and possible origins of sensitivity to chemicals at low levels are discussed. Both clinical observations and evidence for alternative physiologic and psychogenic mechanisms are explored. Implications and challenges for public policy in the areas of alternative employment and housing, compensation, and the regulation of chemicals are addressed.

INTRODUCTION

Chemical exposures are endemic to our modern industrial society. People who believe they are chemically sensitive are caught up in an acrimonious cross fire among several different groups of physicians--traditional allergists; clinical ecologists; and in some cases, ear, nose and throat specialists; occupational physicians; and others. This acrimony is fueled by different medical paradigms of the definition, diagnosis, and treatment of disease or symptoms associated with exposure to low levels of chemicals in food and water, the outdoor environment, the work environment, indoor air, and consumer products. Legal conflicts further complicate the associated scientific and medical differences as attempts by "chemically sensitive" persons to obtain workers' compensation, disability payments, and damage awards from employers and from the producers and users of chemical products result in an adversary system that draws medical practitioners un-willingly into the center of the conflict. Further exacerbating the situation are the insurance industry and employers, who seek to reduce costs for medical care; their involvement continues the volatile history of economic tugs-of-war characteristic of health care in general. "Chemically sensitive" patients seek medical care and consideration from traditional medical practitioners, many of whom are ill equipped or reluctant to provide the painstaking and time-consuming attention that is required for this condition.

Much, but by no means all, of the anecdotal evidence for chemical sensitivities has been reported by clinical ecologists--physician practitioners whose clinical practices have come under intense criticism. However, chemical sensitivity is by no means the exclusive property of clinical ecology. The fields of occupational and environmental medicine contain sufficient examples to suggest a real medical problem.

CHEMICAL EXPOSURES AND SENSITIVE POPULATIONS

Groups sensitive to low-level exposure

A review of the literature on exposure to low levels of chemicals reveals four groups or clusters of people with heightened reactivity:

1. Industrial workers;
2. Occupants of "tight buildings", including office workers and school children;
3. Residents of communities whose air or water is contaminated by chemicals;
4. Individuals who have had personal and unique exposures to various chemicals in domestic indoor air, pesticides, drugs and consumer products.

**Excerpted from Ashford N.A. and Miller C.S. *Chemical Exposures: Low Levels and High Stakes*, New York, Van Nostrand Reinhold 1991.

[1]Reprinted from *Quality of the Indoor Air Environment*, (1992). London, Selper Ltd., pp 49-70, with permission of publisher.

These four groups are listed for comparison in Table 1. Note that they differ in professional and educational attainment, age and sex, and the mix and levels of chemicals to which they are exposed, but that all have multiple symptoms involving multiple organ systems with marked variability in the type and degree of those symptoms. Symptoms are often "subjective". For example, central nervous system (CNS) symptoms such as difficulty concentrating or irritability are common, and physical examinations are frequently unremarkable for individuals in each category. Careful analysis of these groups may reveal differences that can illuminate the etiologies and suggest effective therapeutic options for the myriad problems comprising chemical sensitivity. These differences also may create a referral or selection bias such that members of the four groups present themselves preferentially to different medical practitioners: some may consult occupational health physicians, others primary care physicians, and still others clinical ecologists or allergists.

Problems experienced by people in tight buildings, by industrial workers in a particular workplace, or by the residents of a contaminated community often occur within a relatively short time period--perhaps weeks or a few months. These problems may occur after a recognized event such as the installation of new carpeting, relocation to a new workplace, or changes in workplace or community exposures. The temporal cohesiveness of exposures and problems can contribute to the recognition of the problem as real. Acceptance of these problems as bona fide physical disease may also be facilitated by the recognition that these problems are widespread in nature and are not simply limited to what some observers would describe as malingering employees, hysterical housewives and workers experiencing mass psychogenic illness.

Noteworthy is the fact that individuals in such demographically divergent groups as those in Table 1, including industrial workers, office workers, housewives, and children, report similar polysymptomatic complaints triggered by chemical exposures. Perhaps some common thread unites these individuals. The similarities of both their medical complaints and their exposure histories may be more than coincidental.

In a survey of some 6,800 persons claiming to be chemically sensitive, 80 percent asserted they knew "when, where, with what, and how they were made ill" [1]. Of the 80 percent, 60 percent (that is, almost half of those who replied) blamed pesticides. The respondents to the survey were self selected, and the results may be interpreted with caution. Nevertheless, the results indicate that future surveys of persons with different exposure histories and symptoms might contribute to an understanding of underlying mechanisms and causes.

In some chemically sensitive patients, no single, identifiable, "high-level" exposure seems to have been associated with the onset of their difficulties. Exposures may have occurred but were not recognised or remembered. Some observers suggest that repetitive or cumulative lower-level exposure events may lead to the development of sensitivities. Still others implicate genetic predisposition, pregnancy, major surgery with anaesthesia, physical trauma, or major psychological stress as contributors to the illness.

TABLE 1. Chemically Sensitive Groups

Group	Nature of Exposure	Demographics
Industrial Workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
Tight-building occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white collar office workers and professionals; 20 to 65 years old; school children
Contaminated communities	Toxic waste sites; aerial pesticide spraying; ground water contamination; air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs, and pesticides	70-80% females; 30-50 years old (Johnson and Rea, 1989); white middle to upper middle class professionals

Types of sensitivity

The different meanings of the term *sensitivity* are, at least partially responsible for the confusion surrounding chemical sensitivity.

Individuals differ in their responses to increasing doses of a toxic substance. The underlying causes of inter-individual variability include age, sex, and genetic make-up; lifestyle and behavioral factors, including nutritional and dietary factors, alcohol, tobacco and drug use; environmental factors; and preexisting disease [2]. In the classical, toxicological use of the word *sensitivity*, those individuals who require relatively lower doses to induce a particular response are said to be more sensitive than those who would require relatively higher doses before experiencing the same response [3]. A hypothetical distribution of sensitivities, that is, the minimum doses necessary to cause individuals in a population to exhibit a harmful effect, is shown in curve A in Figure 1. (If we plot the cumulative number of individuals who exhibit a particular response as a function of dose, we generate a population dose response curve; see curve A in Figure 2). This distribution describes the traditional toxicological concept of sensitivity. Curve A in Figure 1 illustrates that health effects of classical diseases are seen in a significant portion of the normal population at a certain dose; the sensitive and resilient populations are found in the tails of the distribution. (Of course, not all toxic substances have large variances or significant tails.) Painstaking scientific research and removing the effects of confounding variables have resulted in the discovery of sensitive individuals at levels heretofore considered safe. Recent work on lead [4] and benzene [5] are just two examples. For the sensitive person, avoidance of low level exposures generally lead to improvement, or at least to the arrest of the development of the disease.

A second meaning of the word *sensitivity* appears in the context of classical IgE-mediated allergy (atopy). IgE is one of five classes of antibodies made by the body and is, from the perspective of classically allergic individuals, the most important antibody. Atopic individuals have IgE directed against specific environmental incitants, such as ragweed or bee venom. Positive skin tests in these individuals correlate with a rapid onset of symptoms when they are actually exposed to those allergens. The atopic individual exhibits a reaction, whereas nonallergic persons do not, even at the highest doses normally found in the environment. A hypothetical sensitivity distribution for an atopic effect is shown in curve B of Figure 1, and the dose-response curve derived from that distribution is found in curve B of Figure 2.

Allergists include in the term *allergy* well-characterized immune responses that result

from industrial exposure to certain chemicals, such as nickel or toluene diisocyanate (TDI). Most allergists refer to such responses as *chemical sensitivity*, and reserve this term for responses that have a distinct immunological basis, preferring to use a term such as *chemical intolerance* for nonimmunological responses to chemical.

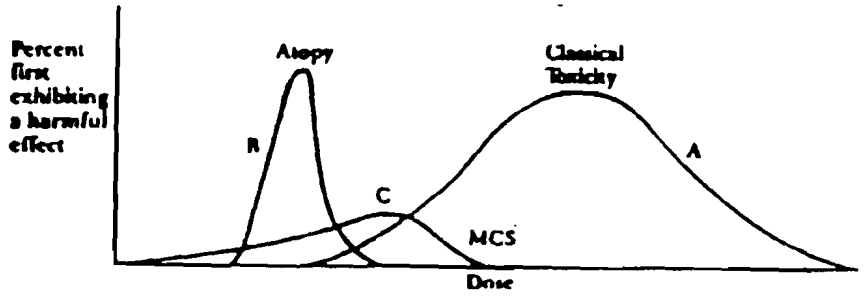


FIGURE 1. Hypothetical distribution of different types of sensitivities as a function of dose. Curve A is a sensitivity distribution for classical toxicity, e.g., to lead or a solvent. Sensitive individuals are found in the left-hand tail of the distribution. Curve B is a sensitivity distribution of atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom. Curve C is a sensitivity distribution for individuals with multiple chemical sensitivities who, because they are already sensitized, subsequently respond to particular incitants, e.g., formaldehyde or phenol.

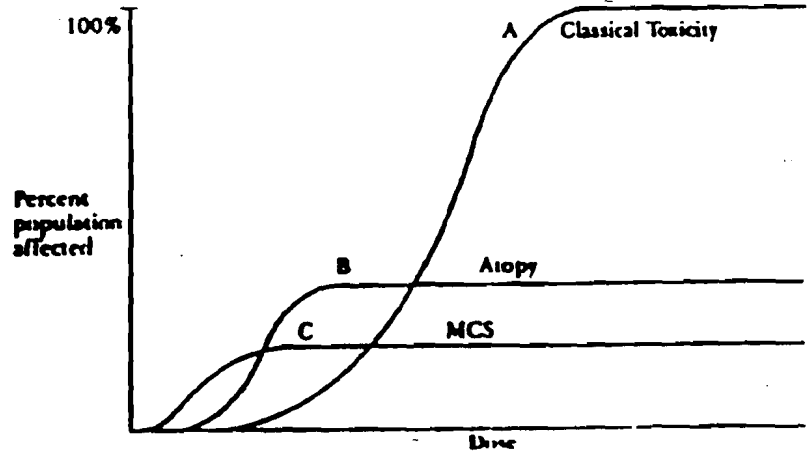


FIGURE 2. Hypothetical population dose-response curves for different effects. Curve A is a cumulative dose-response curve for classical toxicity, e.g., to lead or a solvent. Curve B is a cumulative dose-response curve for atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom. Curve C is a cumulative dose-response curve for individuals with multiple chemical sensitivities who, because they are already sensitized, subsequently respond to particular incitants, e.g., formaldehyde or phenol.

Patients suffering from multiple chemical sensitivities may be exhibiting a third and entirely different type of sensitivity. Their health problems often (but not always) appear to originate with some acute or traumatic exposure, after which the triggering of symptoms and observed sensitivities occur at very low levels of chemical exposure. The inducing chemical or substance may or may not be the same as the substances that thereafter provoke or "trigger" responses. (Sometimes the inducing substance is described as "sensitizing" the individual and the affected person as a "sensitized" person.) Reactions may sometimes be observed at incitant levels similar to those to which classically sensitive and atopic patients respond. Unlike classical toxicity, however, here the effects of low-level exposures are not simply those effects observed in normal populations at higher doses. The fact that normal persons--for example, most doctors--do not experience even at *higher* levels of exposure those symptoms that chemically sensitive patients describe at much lower levels of exposure probably helps to explain the reluctance of some physicians to believe that the problems are physical in nature. (Although this also describes atopy, here the sensitivity is not IgE mediated.) To compound the problem of physician acceptance of this illness, multiple organ systems may be affected, and multiple substances may trigger the effects. Over time, sensitivities seem to spread, in terms of both the types of triggering substances and the systems affected [6].

Avoidance of the offending substances is usually effective but much more difficult to achieve for these patients than for classically sensitive patients because symptoms may occur at extremely low doses and the exposures are ubiquitous. Adaptation to chronic low-level exposure with consequent "masking" of symptoms (discussed more fully later) may make it exceedingly difficult to discover these sensitivities and unravel the multifactorial triggering of symptoms. A hypothetical sensitivity distribution for a single symptom for the already chemically sensitive person in response to a single substance trigger is shown in curve C of Figure 1, and the corresponding dose-response curve is shown in curve C of Figure 2. It should be emphasized, however, that individuals who become chemically sensitive may have been exposed to an initial priming event that was toxic, as classically defined. Conceivably, exposure to certain substances, such as formaldehyde, might elicit all three types of sensitivities.

KEY CONCEPTS

A working definition for multiple chemical sensitivity

Given the multitude of environmental exposures (both chemical and food) that allegedly can result in a seemingly endless array of physical and mental syndromes and the frequent absence of findings on routine physical examination, the practitioner who sees the patients with their divergent and unfamiliar litany of complaints is at great disadvantage in trying to diagnose the condition.

To circumvent this problem, we propose the following *operational* definition of multiple chemical sensitivity, a definition that is based upon environmental testing:

The patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by rechallenge, after an appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge.

Challenges conducted for research purposes should be performed in a double-blind, placebo-controlled manner. This definition embodies the approach to discovering environmental causation that was developed by Randolph. Randolph originated the idea of an environmental unit employing what he terms "comprehensive environmental control" as both a diagnostic and therapeutic tool for dealing with these patients. Briefly, this technique involves placing the patient in a specially constructed environment devoid of materials that off-gas; avoiding the use of drugs, cosmetics, perfume, synthetic fabrics, pesticides, and similar substances; and having the patient fast for a period of days until symptoms resolve. This initial period of avoidance and fasting requires approximately 4 to 7 days on the average. During this time, the patient exhibits withdrawal symptoms such as headache, malaise, irritability, or depression. At the end of this time, the patient's symptoms, if environmentally related,

should clear, provided that end-organ damage has not occurred. Next, individual foods are reintroduced, one per meal, over a two- to three-week period. Following this, the patient is placed on a rotating diet of "safe" foods (i.e., foods that did not provoke symptoms for that particular patient). Finally, the patient is challenged with very low levels (levels routinely encountered in daily living) of common chemicals. Those exposures, both food and chemical, that induce symptoms are to be avoided.

We feel strongly that this operational definition is essential to resolving, once and for all, the debate about whether an individual's symptoms are or are not environmentally induced. An environmental unit is necessary for scientific validation of the concept of chemical sensitivity. Because of the expense and time required by patients and physicians alike, a unit should not be used for all patients. Such stringent measures are not necessary for most patients. For severe cases, however, no alternative is available at present, and only from firsthand observation of hospitalized patients can physicians have the opportunity to understand this illness better. In time, as more clinical data on these patients accumulate, physicians may be able to diagnose this disorder on the basis of the patient's history and a few key laboratory tests. For now, reliance must be placed on rigorous study in an environmental unit. Ultimately, a *phenomenological* definition may emerge that allows physicians to diagnose, at least tentatively, chemical sensitivity based on a history of a specific sensitizing event (such as a pesticide exposure) followed by evidence of chemical and food sensitivities, multisystem effects, improvement after avoidance of exposure, and similar experiences of persons with like histories.

The environmental unit is the gold standard against which all other diagnostic approaches and screening techniques should be measured. An environmental unit is necessary in more severe cases, such as those who have failed outpatient attempts at management or for patients with seizures, suicidal tendencies, incapacitating migraine headaches, arrhythmias, or other problems requiring continuous vigilance. However, most individuals can remain outpatients while they are guided through an elimination diet, avoidance of possible chemical incitants, and rechallenge with suspected offenders.

An enormous number of diagnostic and therapeutic modalities have been adopted by clinical ecologists in order to screen for and treat this illness, many of them lacking scientific verification. The gold standard--comprehensive environmental control with the use of an environmental unit--must be separated from the "fool's gold" of some of the more outlandish and untested diagnostic and therapeutic modalities. This is not to say that certain of those approaches are not now efficacious or may not "pan out" in the future, but many await and need critical scientific appraisal.

Adaptation

One of the difficulties the observer encounters in trying to understand multiple chemical sensitivity is the ostensible lack of a central concept or unifying theory. Such a unifying theory does exist and revolves around the concept of adaptation, known in other contexts as *acclimation* or *acclimatization, habituation, developing tolerance*, and even *addiction* (which we will explain later). Randolph used the terms *adaptation* and *addiction* most often. However, reference to one of the other words may make grasping the concept easier. *Acclimatization* is a widely used term in occupational health which refers to workers gradually becoming accustomed to exposures on the job, for example, to heat stress. Understanding adaptation is important here for two reasons: (1) adaptation makes difficult the discovery of the effects of a particular exposure on the body, and (2) chemical exposures may adversely impact adaptation mechanisms and thus lead to illness.

That human beings respond to chronic exposure to environmental challenges by adapting, acclimating, acclimatizing, or even becoming addicted is widely recognized for a variety of substances. Most would agree that the use of narcotics, alcohol, nicotine, and even caffeine can be addicting. For example, the first cigarette ever smoked might be associated with eye and throat irritation, but over time, with more cigarettes, most individuals adapt, and primarily the pleasurable effects of nicotine on the brain are experienced. After months or years, more cigarettes (or alcohol or caffeine or drugs) may be required for the same amount of lift. The

individuals may exhibit addictive behavior seeking cigarettes more frequently. Subsequently, quitting cigarettes (alcohol, caffeine, or drugs) may lead to withdrawal symptoms including irritability, drowsiness, fatigue, moodiness and headache. After individuals have quit smoking, they may find themselves supersensitive to others' smoke (the forgotten eye and throat irritation reappear after a period of avoidance).

Occupational health presents many examples in which acclimatization, inurement, or tolerance to a substance is known to develop, for example, exposure to ozone, nitroglycerin and solvents. Solvents are among the chemicals most frequently implicated by chemically sensitive patients who attribute the onset of their illness to a particular exposure. Molhave and associates [7] exposed individuals who had previously complained of sick building syndrome symptoms to a mixture of 22 volatile organic compounds common in indoor air, predominantly solvents, for 2 3/4 hours. Levels were much lower than occupational health standards required and in the range of levels found in tight buildings. These healthy but sensitive subjects complained of nasal and throat irritation and inability to concentrate at levels of solvents far below permissible occupational exposure levels. A similar study, using health subjects who had not previously complained of symptoms, showed no effect on the ability to concentrate [8].

Chemically sensitive patients commonly report central nervous system symptoms at solvent levels as low as those used by Molhave and lower. Their complaints are consistent with the recognized health effects of these substances, albeit the levels of exposure that trigger symptoms in these patients may be lower by orders of magnitude.

According to Randolph [9] the stimulatory effects of solvents may be pleasant or unpleasant, depending upon the person and the exposure. Initially, a normal individual exposed to solvents may experience being alert, enthusiastic, energetic, and witty and may sustain this level for long periods, while a chemically sensitive person may progress quickly to feeling tense, jittery, argumentative, sensitive, and overly responsive and experience chills or flushing. Very sensitive individuals may become manic or develop seizures.

During withdrawal, symptoms for relatively healthy individuals may be only mild, localized symptoms resembling an allergy, for example, a runny or stuffy nose, coughing, wheezing, eczema, hives, diarrhea, and eye and ear symptoms. However, the response is not actually an allergic one; there is no evidence that IgE plays a role. If withdrawal is more severe, fatigue, depression, muscle and joint aches, headache, and a rapid or irregular heart rate may ensue. At more advanced stages in very sensitive individuals, confusion, indecision, and apathy can occur with comprehension and concentration becoming impaired. The most severe stage may be attended by stupor, delusions, and hallucinations. From a clinical viewpoint, Randolph's model could serve as a useful framework for following the progression of these patients' symptoms. Many patients with chemical sensitivity seem to experience the more advanced stages of stimulation and depression in the model. According to Randolph, when they are deadapted and then exposed to a single incitant, the stepwise, sinusoidal progression up through stimulatory levels and back down through withdrawal levels can be observed. In normal daily life, exposures overlap and discrete stages may not be discerned.

Studies of xylene (one of the most prevalent solvents in indoor air), conducted by Riihimaki and Savolainen [10], demonstrate that its effects are attenuated as exposure continues, presumably due to adaptation.

Symptoms of exposure to many chemicals, whether inhaled or ingested, appear to follow a biphasic pattern similar to that for solvents. Adaptation is characterised by acclimatization (habituation, tolerance) with repeated exposures that result in a masking of symptoms. Withdrawal occurs when exposure is discontinued. Once a person has adapted, then the experimental consequences are that further exposures have very little additional effect and therefore may not be observed. The observer may not be able to witness the stimulatory or reactive event because a kind of "saturation" effect has set in.

Adaptation and withdrawal may occur for a wide variety of organic and inorganic substances in many physical forms, including various dusts and fumes, solvents, nitroglycerin, ozone, and foods.

An individual is exposed to a variety of substances at different times with varying frequency, duration, and intensity of exposure for each of these substances and with varying frequency and duration of reduction in or cessation of exposure for each substance. The individual may be in different stages (stimulatory or withdrawal) simultaneously for different substances. These stages may overlap and interfere with attempts to observe cause-and-effect relationships. Adaptation may mask some symptoms or effects, while other physiological alterations, some harmful, continue.

Comprehensive environmental control, that is, an environmental unit, can overcome the masking effect of adaption and the problems of overlapping exposures that result in overlapping responses to multiple agents. The environmental unit can back up or reverse the experience of adaptation and allow the investigator to monitor toxicity in progress. The advantages that dynamic toxicology of this nature has over conventional methods for determining toxicity include facilitating detection of subclinical, prepathological effects of chemicals and providing more than just a snapshot of an individual's response to substances. Removing the person from interacting, time-dependent stimuli in this way allows the unravelling of multiple causes. The environmental unit is an essential tool. Many carefully conducted studies of chemical effects that have had negative or equivocal outcomes may be flawed by their failure to take adaptive mechanisms into account. The consequences of such an oversight could be major.

The detailed description of an environmental unit is beyond the limits of this discussion. In essence, by employing construction materials, furnishings, and clothing that are less likely to off-gas, and with proper ventilation and air filtration, very low levels of volatile organic compounds (for example, from synthetics) can be maintained inside the unit. To create and operate a unit that is as free as possible from chemical pollution requires knowledge, precision, and vigilance while working with architects, ventilation engineers, contractors and their suppliers, nurses, dieticians, food and water suppliers, and maintenance and custodial staffs.

MECHANISMS OF MULTIPLE CHEMICAL SENSITIVITIES

A useful review of this topic can be found in Ashford and Miller [11] and in Bell [12]. The limited data available at this time suggest that any mechanism or model that would purport to explain the syndrome of multiple chemical sensitivities would need to address the features most closely associated with this illness:

1. Symptoms involving virtually any system in the body or several systems simultaneously;
2. Differing symptoms and severity in different individuals, even those with the same exposure;
3. Induction (that is, sensitization) by a wide range of environmental agents;
4. Subsequent triggering by lower levels of exposure than those involved in initial induction of the illness;
5. Concomitant food intolerances, estimated to occur in a sizable percentage of those with chemical sensitivities;
6. "Spreading" of sensitivity to other, often chemically dissimilar substances; each substance may trigger a different constellation of symptoms;
7. Adaptation (masking), that is, acclimatization to environmental incitants, both chemical and food, with continued exposure; loss of this tolerance with removal from the incitant(s); and augmented response with reexposure after an appropriate interval (for example, 4 to 7 days);
8. An apparent threshold effect referred to by some (including certain traditional allergists we interviewed) as the patient's *total load*. Total load is a theoretical construct that has been invoked by clinical ecologists to help explain why an individual develops this syndrome at a particular time. Illness is said to occur when the total load of biological, chemical, physical and psychological stressors exceeds some threshold for the patient. This concept has emerged from clinical observations; no direct experiments have been done to test its validity in humans; however, animal models do exist. The concept aligns with Selye's work on the general adaptation syndrome [13].

The most frequently cited theories to explain chemical sensitivity involve the nervous system, the

immune system, or the interaction between them, because these two systems most clearly link the external environment and the internal milieu [14]. The rapid responsiveness of these systems also makes them attractive candidates because symptoms of food or chemical sensitivity have been reported to develop within seconds of exposure.

Mechanisms involving the limbic system

The hypothalamus (part of the limbic system) has attracted considerable attention because it is the focal point in the brain where the immune, nervous, and endocrine systems interact [14]. Bell notes that assuming a direct cause-and-effect relationship would be premature, but that the hypothalamus could mediate food and chemical addictions in patients with multiple chemical sensitivities. The olfactory system has known links to the hypothalamus and other parts of the limbic system, which has led Bell [14] to speculate that "the olfactory system, hypothalamus and limbic system pathways would provide the neural circuitry by which adverse food and chemical reaction could trigger certain neural, psychological and psychiatrical abnormalities". Many different chemicals have been reported by clinical ecologists to trigger food cravings, binges, violence, or hypersexual activity. A model involving the hypothalamus could help to explain such behavioral changes in response to chemical exposures.

The limbic system, a phylogenetically ancient part of the brain, is present in all mammals. It influences the organism's interaction with its environment in many subtle ways essential for preservation of the individual, its offspring and the species. Strong odours and even milder ones may provoke increased electrical activity in the amygdala and hippocampal areas of the limbic system [15]. Subsensory exposure to chemicals can cause protracted, if not permanent, alterations in the electrical activity of the brain, beginning first with the most sensitive structures, particularly that portion of the amygdala that analyses odours [16]. The amygdala is involved in feelings and activities related to self-preservation, such as searching for food, feeding, fighting and self-protection [17]. Lesions in the septal area may cause hyperresponsiveness to physical stimuli (such as touching, sounds, or temperature changes), hyperemotionality, loss of motivation, excessive sugar and water intake, and fear of unfamiliar situations [18].

The hippocampus appears important for laying down new memories and thus is essential for learning [19]. Hippocampal lesions may cause difficulty in retaining recent memories [18]. Learning and memory decrements are a frequent consequence of exposure to toxic substances, and some researchers view the hippocampus as a prime target for such toxins [20, 21].

The most vital component of the limbic system, the hypothalamus, governs: (1) body temperature via vasoconstriction, shivering, vasodilation, sweating, fever and behaviors such as moving to a cooler or warmer environment or putting on or taking off clothing; (2) reproductive physiology and behavior; (3) feeding, drinking, digestive and metabolic activities, including water balance, addictive eating leading to obesity, and complete refusal of food and water leading to death; (4) aggressive behavior, including such physical manifestations of emotion as increased heart rate, elevated blood pressure, dry mouth and gastrointestinal responses [19].

The hypothalamus is also the locus at which sympathetic and parasympathetic nervous systems converge. Many symptoms experienced by patients with food and chemical sensitivities relate to the autonomic (sympathetic and parasympathetic) nervous systems; for example, altered smooth muscle tone produced Raynaud's phenomenon, diarrhea, constipation and other symptoms.

The hypothalamus appears to influence anaphylaxis and other aspects of immunity [22]. Likewise, antigens may affect electrical activity in the hypothalamus [23]. Thoughts arising in the cerebral cortex that have strong emotional overtones can trigger hypothalamic responses and recreate the physical effects associated with intense anger, fear and other feelings. To implement its effects, the hypothalamus not only has a direct electrical output to the nervous system but also produces its own hormones, many of which stimulate or inhibit the pituitary's production of hormones [19].

Lesions in the limbic region may be associated with irrational fears, feelings of strangeness or unreality, wishing to be alone and sadness [24]. A feeling of being out of touch with or out of control of one's

feelings and thoughts, not unlike that described by many patients with chemical sensitivity, may be perceived.

The dynamic involvement of the hypothalamus and limbic system in virtually every aspect of human physiology and behavior makes injury to these structures an intriguing hypothesis to explain chemical sensitivity's myriad manifestations. Bell [25] hypothesizes that chemically sensitive patients may have olfactory-limbic-temporal pathways that are more easily "kindled". In other words, a small signal or insult would more readily trigger firing of nerve cells in brain regions where kindling was present. Kindling might be enhanced by genetic endowment, prior environmental exposures, psychological stress, hormonal variations or other factors.

Immunologic mechanisms

Immunological alterations are another possible explanation for multiple chemical sensitivities. Most of us have been taught that the immune system evolved to defend our bodies against microorganisms and other "foreign invaders". Actually, the immune system may have evolved to help control the body's internal milieu. Thus, its purpose is not simply to ward off infections but also to carry out precise regulatory interactions between the immune system, endocrine system and nervous system. Animal experiments demonstrate immunotoxicity from halogenated aromatics, heavy metals and organochlorine pesticides. Accidental human exposures to aldicarb, polybrominated biphenyls (PBBs), dioxin and other toxins also provide data that chemicals can impact the immune system.

Some view environmental illness as a disorder of immune regulation [26]. These authors point to decreased T-lymphocyte helper-suppressor ratios in different populations exposed to environmental toxins. Further studies employing carefully matched controls are needed.

Others report T-lymphocyte activation, particularly increases in Tal positive T-lymphocytes [27]. Relatively low-molecular-weight chemicals can alter native protein, perhaps by acting as haptens, and elicit a sort of autoimmune response to that altered protein. Formaldehyde [28], trimellitic anhydride [29], isocyanate [30], hydantoins [31], which are present in many drugs and foods, and hydrazine [32], which occurs in mushrooms, plastics, pesticides, tobacco smoke and various drugs, have all been reputed to cause immune derangement, possibly by such a mechanism.

Broughton and Thrasher [33] report the development of antibodies to formaldehyde-albumin conjugates, evidence of immune system activation (activation marker Tal on T-lymphocytes), low titers of a variety of autoantibodies, and altered IL-I (interleukin) production in these individuals, suggestive of "subtle but chronic activation of the immune system" [34]. They state that similar alterations occur in patients exposed to chlordane (a termiticide) and solvents in drinking water. Testing blood from symptomatic patients with a history of chemical exposure, Broughton and Thrasher noted a much higher incidence of autoantibodies among these patients than among controls [34]. Individuals exposed to formaldehyde, trichloroethylene and chlordane were tested for antinuclear antibody (ANA) and autoantibodies to parietal cells, smooth muscle, brush border, mitochondria and myelin. The clinical significance of some of these antibodies, particularly low titers, is not known, but the differences between exposed and unexposed groups are striking and warrant further investigation. Exposed groups were three to four times more likely than controls to have one or more autoantibodies present. In addition, the incidence of autoantibodies appeared higher when exposure was ongoing than when some time had elapsed. Future governmental and scientific investigations should include measurement of T- and B-cell numbers, Lymphocyte activation and other relevant immune parameters as possible indices of toxicity. It is important that such studies employ carefully matched control subjects.

Biochemical Mechanisms

Some physicians have noted vitamin and mineral abnormalities in many of their patients [35, 36]. Their detractors argue that these patients are often sick, debilitated and malnourished, and therefore such findings are not surprising. Such a contention is difficult to disprove, even if it were incorrect.

Individuals who have defective enzyme detoxification systems may be more susceptible to

low level exposures. Rea has noted that many of his chemically sensitive patients have decreased levels of detoxifying enzymes, such as glutathione peroxidase.

Levine [37] has proposed that environmental sensitivities are the result of toxic chemicals reacting with cell constituents to create free radicals (which are formed when a molecule loses an electron). He hypothesizes that if an antioxidant molecule (such as vitamins A, C, E and selenium) is not present nearby to supply the missing electron, then an electron may be removed from an unsaturated lipid (lipid peroxidation) in a cell membrane, leading to membrane damage, release of prostaglandins and other inflammatory mediators, and formation of antibodies to chemically altered tissue macromolecules.

Rea [38] hypothesizes that blood vessel constriction, inflammation or leakage in multiple organ systems may explain the bizarre combinations of symptoms in these patients. In his view, particular complaints may simply mirror the site and size of affected blood vessels. The walls of blood vessels contain smooth muscle. Rea notes that if a patient's symptoms are not explainable by vascular involvement, then other tissues containing smooth muscle such as the respiratory, gastrointestinal and genitourinary systems are frequently implicated [39].

Possible psychogenic mechanism

Two separate issues arise in the context of possible psychiatric origins or contributions to chemical sensitivity. The first relates to the plausibility, nature and extent of these contributions; the second concerns the most prudent approach toward diagnosis and treatment of the patient when both physiological and psychological factors might be involved.

Psychological symptoms are not necessarily psychological in origin. Advances in biological psychiatry focus on genetic and biochemical factors as contributors to central nervous system dysfunction and behavioral disturbance. Environmental exposures can also have psychological sequelae.

The symptoms of low-level chemical exposure may include depression, difficulty concentrating, anxiety, peculiar bodily sensations, headaches and other subjective symptoms. Patients with multiple chemical sensitivities often report that before they understood what was causing their symptoms they felt as if they could not trust their own bodies or feelings. At any moment, they might feel fine, making plans and commitments for the future; then, the next day or even later the same day, they might feel lethargic, unmotivated, headachy, sleepy and depressed, as if they had the flu. Suddenly, they are unable to fulfil commitments made when they felt energetic. These ups and downs are frequently interpreted by psychiatrists as responses to psychosocial stresses, and patients may be willing to accept such insights because they lack a better explanation. In contrast, patients who have been worked up in an environmental unit often say they are amazed to find direct, clear-cut, cause-and-effect relationships between their symptoms and various foods and chemicals.

Many of the chemicals these patients implicate as triggering their symptoms are solvents, pesticides and other substances whose primary target organ, in terms of classical toxicity, is the brain. Interestingly, these individuals who "react" to levels well below those heretofore considered toxic also complain of central nervous system symptoms. Therefore, their complaints are in many respects consistent with known toxic actions of these substances, albeit the levels of exposure triggering their reactions are quite different.

That odor conditioning could occur in selected cases is certainly possible. However, patients experience reproducible symptoms to specific chemical exposures (1) often before the odor is perceived (for example, some patients experience symptoms in a particular room or building without detecting an odor, only to learn later that the facility had been recently sprayed with pesticides [38]), (2) with their noses clamped during provocative testing, and (3) when anosmia is present [40]. These observations weigh heavily against classical conditioning as any more than a partial explanation in certain patients.

It has been suggested that inhaled chemicals may irritate trigeminal free nerve endings in the nose [42]. Irritation causes a reflexive, involuntary disruption of breathing, a phenomenon familiar to anyone who has inhaled smelling salts. Although

trigeminal irritation could explain certain symptoms, such as breathlessness or faintness, in response to pungent olfactory stimuli, it does not explain the entire range of symptoms reported by these patients, often in response to odors that are barely discernible. In addition, patients describe feeling symptoms moments after exposure via introdermal or sublingual routes of administration. Likewise, suppositories placed in contact with mucosal surfaces may provoke onset of symptoms in these patients. Thus, many avenues of exposure may lead to reactions in these patients.

Patients with chemical sensitivities experience very specific and reproducible constellations of symptoms in response to particular exposures. For example, in one individual, diesel exhaust might trigger sleepiness, mental confusion and ravenous hunger; rest room deodorizers might be associated with nervousness and irritability; and exposure to a pesticide might be associated with rage followed by uncontrollable crying. Although conditioning could play a role, the fact that responses are *specific* for particular exposures suggests otherwise.

Results of psychological tests may be misleading in chemically sensitive patients. For example, the Minnesota Multiphasic Personality Inventory (MMPI), a widely used psychological instrument, includes questions concerning peculiar bodily sensations, feelings of inappropriateness, depressed feelings and many other symptoms, any of which could result from chemical exposures. The chemically sensitive patient who has such symptoms may "read out" as depressed, hypochondriacal or hysterical on MMPI scales when, in fact, depression, hypochondriasis and hysteria might not be the cause but rather the result of their food and chemical sensitivities.

Some are of the opinion that multiple chemical sensitivity patients adhere to a "belief system" that chemicals are the cause of their health problems [43] and advocate systematic deprogramming of the patients to purge them of their beliefs, while others believe that no pyschotherapeutic intervention will help these patients [45].

Some psychiatrists strongly feel that individuals with multiple chemical sensitivities suffer from atypical depression, hypochondriasis, post-traumatic stress disorder, hysteria, panic disorder, conversion disorder or combinations of these [46, 47]. It must be remembered that psychological symptoms are not necessarily psychogenic in origin. Future research that attempts to distinguish between psychogenic and chemical causes for chemical sensitivity should be conducted using an environmental unit and take into account the effect of adaption.

DIAGNOSIS AND TREATMENT

As with most fields in medicine, meticulous history taking is the most important element in making a diagnosis. However, history taking for multiple chemical sensitivities involves obtaining a chronology not only of illness but of exposures as well. "Although the physical examination is an integral part of all medical investigation, 'examination of the environment' of a patient tends to be relatively more rewarding" [48].

An adequate exposure history with attention given to pinpointing when symptoms began in relation to other factors (for example, drugs, chemical exposures, job changes, household moves, operation and hobbies) is essential. Concurrent illness in other household members, co-workers, and even pets may provide clues. This time-consuming detective work is the *sine qua non* for discovering an inciting exposure. Properly designed patient questionnaires may facilitate the process by enabling the patient to engage in the detective work as well. Questions concerning the patients' likes or dislikes for certain odours may be revealing, because aversion to particular odors has been noted commonly among patients who have multiple chemical sensitivities [9].

In addition, patients can prepare a chronology or time line of major events such as household moves, job changes, surgeries, and pregnancies and the onset and duration of symptoms or illness. Similarly, a daily log of activities or exposures that notes any symptoms may facilitate recognition of patterns.

The more symptoms and the more systems of the body affected, especially the nervous system, and the more these symptoms fluctuate in intensity, the stronger should be the physician's suspicion of multiple chemical sensitivities. Johnson and Rea

[35] report that the average patient entering the Dallas environmental unit has five symptoms complaints, many of which are neurological. Industrial workers with multiple chemical sensitivities exhibit similar constellations of symptoms [49]. A history of multiple "idiosyncratic" drug reactions or alcohol or food intolerance or cravings may also be suggestive. "Allergies" or intolerances to multiple drugs are reported by many patients.

The physical exam, traditionally an important diagnostic tool, disappointingly is often normal in these patients. Symptoms or signs may occur only with exposure. Injury may be subclinical and prepathological. Laboratory findings may be normal or, if abnormal, provide no pattern or clue that seems to have clinical relevance. Altered helper-suppressor T-lymphocyte ratios and the presence of autoimmune antibodies may be suggestive but are not diagnostic. Subtle signs of vasculitis can be noted in some; spontaneous bruising, petechiae, and cold or blue extremities (Raynaud's phenomenon) may occur.

As discussed earlier, the gold standard for diagnosing chemical hyperreactivity in a patient is the environmental unit, coupled with fasting. Although this approach may be too costly and time-consuming for the average patient, for the very ill it may be the only way to unravel this multifactorial, polysymptomatic illness. Eventually, biomarkers may be developed for chemical sensitivity, especially if the mechanisms of the disease are biochemical or immunological. However, if the nervous or limbic system is key, it may not be possibly to identify biomarkers.

Short of a several-week stay in an environmental unit, can any other approach be used to diagnose chemical and food sensitivities in patients who do not require hospitalization or who may wish to be worked up as outpatients? Certainly an elimination diet can be attempted to identify food incitants. Patients may have difficulty fasting or avoiding common incitants, rotating their foods, or obtaining chemically less contaminated foods. (Even so-called organic foods may not be entirely free of pesticides and other contaminants). Detecting subtle chemical sensitivities while at home is even more difficult. Masking or adaptation to chemicals in one's home environment (such as gas furnace emissions) may go unrecognized. If comprehensive environmental control is attempted at home, major remodelling or overhauling of furniture, heating systems, wardrobe and other major changes may be required in order to achieve a chemically less contaminated environment for the patient. Such interventions done in a hit-or-miss fashion could be costly. Far better would be residences that are relatively "safe" habitats, such as specially constructed trailers or homes in which patients could reside temporarily while they sort out their sensitivities and undergo food and chemical testing.

Clearly, the cost and trouble of such rigorous diagnostic approach may be prohibitive for the average patient with chemical sensitivities. For this reason, provocation-neutralisation has been promoted by ecologists as a way to diagnose and treat at least some of their patients' sensitivities to biological inhalants, foods and chemicals. The evaluation of this and other therapies is beyond the scope of this paper. The interested reader is referred to the book, *Chemical Exposures: Low Levels and High Stakes,* for a fuller discussion [11].

PUBLIC POLICY IMPLICATIONS FOR INDOOR AIR

The discussion above has focused on the description of and scientific issues attending the problems of chemical sensitivity. Although the precise nature of this condition and the underlying mechanisms remain somewhat uncertain and are evolving in nature, the condition seems to be sufficiently well recognized to require attention by government, industry and the medical profession.

Public policy needs to be focused towards two distinct groups: (1) those individuals who could become sensitized as a result of an initiating exposure, and (2) those individuals who have already become sensitized and are now sensitive to chemicals at extremely low levels. Regulations and policies need to be developed to prevent the sensitization of individuals in the first place. Some sensitizing events do not occur in domestic indoor or white-collar work environments, but rather as a result of industrial exposures, hospital exposures or outdoor exposures in contaminated communities. To prevent sensitization in these cases, we need to establish standards protecting against sensitization in

the workplace and ambient environments, as well as sensitization that occurs through exposure to some consumer products, pesticides and pharmaceuticals.

For individuals who are already sensitized, public policy issues must focus on ways to accommodate them by providing chemical-free work environments, schools and housing. For a particular individual, this accommodation will probably need to be temporary in nature, except for those who are severely afflicted. Regulatory and corporate policies are needed to accommodate these individuals in an immediate, humane and understanding manner.

The literature is rich with examples of sensitizing events that occur within the domestic indoor or white-collar work environment, such as those due to new carpeting, cooking stoves and other products or processes articulated in the earlier discussion. In many regulatory systems, the control of indoor air quality falls between the cracks. Regulation may be totally lacking or authority may be fragmented and dispersed throughout several agencies or offices. In order to control problems within the domestic setting, regulations would have to address residential construction, consumer products, ventilation standards and so forth. In most national jurisdictions, we are just coming to grips with the need for a coherent indoor air regulatory policy. Until an appropriate preventive policy does develop, government and industry need to establish guidelines for accommodating sensitized individuals in workplaces, schools and residential housing as well as policies that address issues of disability or compensation.

At first blush, addressing the needs of people who are exquisitely sensitive to chemicals at levels many orders lower than the conventional toxic limits might seem to present an impractical and insurmountable challenge. However, if an aggressive set of initiatives to prevent future sensitization were instituted, then we could eliminate the next generation of sensitive individuals, and the need to accommodate them would become much less burdensome in practice.

REFERENCES

1. National Foundation for the Chemically Hypersensitive, *Cheers*. Wrightsville Beach, NC, 1, 6 (1989).
2. Ashford N. *et al.*, Human monitoring: Scientific, legal and ethical considerations. *Harvard Environmental Law Review*, 8 (2),263-364 (1984).
3. Hattis D. *et al.*, Human variability in susceptibility to toxic chemicals: A preliminary analysis of pharmacokinetic data from normal volunteers. *Risk Analysis*, 7, 415-426 (1987).
4. Bellinger D. *et al.*, Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *New England Journal of Medicine*, 316, 1037-1043 (1987).
5. Rinsky R.A. *et al.*, Benzene and leukemia: An epidemiologic risk assessment. *New England Journal of Medicine*, 316, 1044-1050 (1987).
6. Randolph T., *Human Ecology and Susceptibility to the Chemical Environment*. Charles C. Thomas, Springfield, IL. (1962).
7. Molhave L. *et al.*, Human reactions to low concentrations of volatile organic compounds. *Environmental International*, 12, 167-175 (1986).
8. Otto D. *et al.*, Neurobehavioral and sensory irritant effects of controlled exposure to a complex mixture of volatile organic Ccompounds. *Neurotoxicology and Teratology*, in press (1990).
9. Randolph T. and Moss R., *An Alternative Approach to Allergies*. Lippincott & Crowell, New York (1980).
10. Riihimaki V. and Savolainen K., Human exposure to m-Xylene. Kinetics and acute effects on the central nervous system. *Annals of Occupational Hygiene*, 23, 411-432 (1980).
11. Ashford N.A. and Miller C. S., *Chemical Exposures, Low Levels and High Stakes*. Van Nostrand Reinhold, New York (1991) .
12. Bell I., Environmental illness and health: The controversy and challenge of clinical ecology for mind-body health, *Advances*, 4(3), 45-55 (1987).
13. Selye H., The general adaptation syndrome and the diseases of adaptation. *Journal of Allergy*, 17, 231-247, 289-323, 358-398 (1946).
14. Bell I., *Clinical Ecology*. Common Knowledge Press, Bolinas, CA (1982).

15. Monroe R., Episodic Behavioral Disorders and Limbic Ictus. In: *The Limbic System: Functional Organization and Clinical Disorders*, Doane K. and Livingston K. (eds), Raven Press, New York, p. 251-266 (1986).
16. Bokina A. *et al.*, Investigation of the mechanism of action of atmospheric pollutants on the central nervous system and comparative evaluation of methods of study. *Environmental Health Perspective*, 13, 37-42 (1976).
17. MacLean P., Culminating developments in the evolution of the limbic system: The thalamocingulate division. In: *Organization and Clinical Disorders*, Doan B. and Livingston K. (eds), Raven Press, New York, p.1-28 (1986).
18. Isaacson R., *The Limbic System*. Plenum Press, New York (1982).
19. Gilman S. and Winans S., *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology*. F.A. Davie Company, Philadelphia (1982).
20. United States Congress, Office of Technology Assessment. *Neurotoxicity: Identifying and Controlling Poisons of the Nervous System*, OTA-BA-436, Washington, DC, April (1990).
21. Walsh T. and Emerich D., The Hippocampus as a common target of neurotoxic agents. *Toxicology*, 49, 137-140 (1988).
22. Stein M. *et al.*, The hypothalamus and the immune response. In: *Brain, Behavior and Bodily Disease*, Weiner H. *et al.*, (eds), Raven Press, New York, p. 45-65 (1981).
23. Besedovsky H. *et al.*, Hypothalamic changes during the immune response. *European Journal of Immunology*, 7, 323-325 (1977).
24. MacLean P., The brain in relation to empathy and medical education. *Journal of Nervous and Mental Disease*, 144 (5), 374-382 (1967).
25. Bell I., The Biopersonality of Allergies and Environmental Illness. Paper presented at the Eighth Annual International Symposium on Man and His Environment in health and Disease, Dallas, TX, February 21 (1990).
26. Levin A. and Byers V., Environmental illness: A disorder of immune regulation. In: *Workers with Multiple Chemical Sensitivities*, Cullen M. (ed), Hanley & Belfus, Philadelphia, 2(4), 669-682 (1987).
27. Broughton A. *et al.*, Immunological evaluation of four arc welders exposed to fumes from ignited polyurethane (isocyanate) foam: Antibodies and immune profiles. *American Journal of Industrial Medicine*, 13, 463-472 (1988).
28. Thrasher J. *et al.*, Evidence for formaldehyde antibodies and altered cellular immunity in subjects exposed to formaldehyde in mobile homes. *Archives of Environmental Health*, 42(6), 347-350 (1987).
29. Akiyama K. *et al.*, Hapten-modified Basophils: A model of human immediate hypersensitivity that can be elicited by IgG antibody. *Journal of Immunology*, 133(6), 3286-3290 (1984).
30. Butcher B. *et al.*, Development and loss of toluene diisocyanate reactivity: Immunologic, pharmacologic and provocative challenge studies. *Journal of Allergy and Clinical Immunology*, 70, (4), 231-235 (1982).
31. Kammuller M. *et al.*, Chemical-induced autoimmune reactions and Spanish toxic oil syndrome. Focus on hydantoins and related compounds. *Clinical Toxicology*, 26, (3 4), 157-174 (1988).
32. Reidenberg M. *et al.*, Lupus Erythematosus-like disease due to Hydrazine. *American Journal of Medicine*, 75, 363-370 1983.
33. Broughton A. and Thrasher J., Antibodies and altered cell mediated immunity in formaldeyde exposed human. *Comments in Toxicology*, 2 (3), 155-174 (1988).
34. Broughton A., Biological monitoring of indoor air pollution: A novel approach. *Indoor Air '90, Fifth International Conference on Indoor Air Quality and Climate*, Toronto, Ontario, 2, 145-150 (1990).
35. Johnson A. and Rea W., Review of 200 cases in the environmental control unit, Dalls. Presented at the Seventh International Symposium on Man and His Environment in Health and Disease, February 25-26, Dallas (1989).
36. Roger S., A practical approach to the person with suspected indoor air quality problems. *Indoor Air '90, Fifth International Conference on Indoor Air Quality and Climate*, Toronto, Ontario, 5, 345-349 (1990).
37. Levine S. and Reinhardt J., Biochemical pathology initiated by free radicals, oxidant chemicals and therapeutic drugs in the etiology of chemical hypersensitivity disease. *Orthomolecular Psychiatry*, 12, 166-183 (1983).

38. Rea W. *et al.*, Environmentally triggered large-vessel vasculitis. In: *Allergy and Medical Treatment*, Johnson J. and Spencer J. (eds), Symposia Specialists, Chicago, 185-198 (1975).
39. Rea W., Environmentally triggered small vessel vasculitis. *Annals of Allergy*, 38, 245-251 (1977).
40. Ziem G., Personal communication, November 8 (1989).
41. Shim C. and Williams M., Effect of odors in asthma. *American Journal of Medicine*, 80, 18-22 (1986).
42. Doty R. *et al.*, Olfactory sensitivity, nasal resistance and autonomic function in patients with multiple chemical sensitivities. *Archives of Otolaryngology--Head and Neck Surgery*, 114, 1422-1427 (1988).
43. Staudenmayer H. and Selner J., Post-traumatic stress syndrome (PTSS): Escape in the environment. *Journal of Clinical Psychology*, 43 (1), 156-157 (1987).
44. Selner J., Chemical sensitivity. In: *Current Therapy in Allergy, Immunology and Rheumatology*, B.C. Decker, Philadelphia, 48-52 (1988).
45. Terr A., Personal communication, December 19 (1989).
46. Brodsky C., Multiple chemical sensitivities and other "environmental illness": A psychiatrist's view. In: *Workers with Multiple Chemical Sensitivities, Occupational Medicine: State of the Art Reviews*, Cullen M. (ed), Hanley & Belfus, Philadelphia, 2 (4), 695-704 (1987).
47. Schottenfeld R., Workers with multiple chemical sensitivities: A psychiatric approach to diagnosis and treatment. In: *Workers with Multiple Chemical Sensitivities, Occupational Medicine: State of the Art Reviews*, Cullen M. (ed), Hanley & Belfus, Philadelphia, 2 (4), 739-754 (1987).
48. Randolph T., *Environmental Medicine: Beginnings and Bibliographies of Clinical Ecology*, Clinical Ecology Publications, Fort Collins, CO. (1987).
49. Conn J. *et al*, Patients with multiple chemical sensitivities: Clinical diagnostic subsets among an occupational health clinic population. In: *Workers with Multiple Chemical Sensitivities, Occupational Medecine: State of the Art Reviews*, Cullen M. (ed), Hanley & Belfus, Philadelphia, 2(4), 721-738 (1987).

*POSSIBLE MODELS FOR MULTIPLE CHEMICAL SENSITIVITY: CONCEPTUAL ISSUES AND ROLE OF THE LIMBIC SYSTEM**

CLAUDIA S. MILLER, MD, MS
Assistant Professor, Allergy and Immunology
University of Texas Health Science Centre San Antonio, Texas

INTRODUCTION

It was six men of Hindostan,
To learning much inclined,
Who went to see the elephant,
(Though all of them were blind);
That each by observation,
Might satisfy his mind.

J.G. Saxe

There is an accumulating number of clinical observations concerning patients who report multiple chemical sensitivities (MCS), and investigators who might propose a mechanism or model to explain this syndrome should be aware of these observations. Some observations have come from researchers, some from clinicians, and some from MCS patients. Few of these observations have been tested in a scientific manner. Nevertheless, taken as a whole, they may provide us with important clues about the MCS "elephant". The purpose for reviewing these observations is 1) to provide a common body of data, anecdotal or otherwise, to facilitate discussion of the problem and thereby 2) to enhance the probability of generating fruitful mechanistic hypotheses. Consider this a kind of brainstorming session--an attempt to write all our ideas on the blackboard while suspending judgement about their correctness or utility. Later we can edit them as we learn more.

Remarkably, despite the lack of an accepted clinical case definition for MCS, most physicians who are aware of this problem almost immediately recognize these patients. This process has a gestalt like quality. We must find ways to dissect these clinical intuitions, frame them as hypotheses, and test them in a scientific manner.

Persons who have worked with MCS patients can readily attest that getting involved with their medical problems and lifestyle difficulties can be both time-consuming and exceedingly frustrating, for a variety of reasons. Yet MCS may represent an unprecedented opportunity to further our knowledge of environmental health, psychology and psychiatry, or all of these (depending upon our personal views of the etiology of this problem). Throughout the history of science, the diligent pursuit of rare, serendipitous events has produced enormous yields. Wilson's cloud chamber allowed physicists to capture rare atomic events, providing new information concerning protons, electrons, and other sub-atomic particles. In medicine, rare genetic events have provided valuable clues about the human genome. The diligent study of MCS patients may also lead us toward unanticipated discoveries.

It is hoped that the following observations (and they are *only* observations) will lead to clearer hypotheses and experiments to test those hypotheses. Science is not about "belief". It is about "guess and test", that is, formulating hypotheses that can then be subjected to scientific scrutiny. Many, if not all, of us have strong personal beliefs about chemical sensitivity. Despite our different views, we should nevertheless be able to agree on which hypotheses and mechanisms are most plausible and how to test them in an objective manner.

OBSERVATIONS ON MCS

Induction (Priming or Sensitization)

Onset Following a Major Chemical Exposure. In many cases, MCS appears to follow a major

*Reprinted from Rest, K.M. ed. (1992). *Advancing the Understanding of Multiple Chemical Sensitivity: Proceedings of the Association of Occupational and Environmental Clinics (AOEC) Workshop on Chemical Sensitivity,* Princeton Scientific Publishing Co. Inc., pp 181-202, with permission of the publisher.

exposure to any of a wide range of environmental chemicals. The exposure may occur briefly at high levels or repeatedly or continuously at lower levels. Commonly reported inducing (priming or sensitizing) exposures include pesticides, solvents, or complex mixtures, such as combustion products or indoor air pollutants. However, onset of illness has been attributed to various other events, for example, surgery with anesthesia, pregnancy, extreme stress, or courses of various drugs. In one survey of 6800 persons reporting chemical sensitivities, almost 50% blamed pesticides (National Foundation for the Chemically Hypersensitive, 1989). Between 1984 and 1990, the National Pesticide Telecommunications Network received more than 1000 calls on chemical sensitivity attributed to pesticide exposures (NPTN, 1991). A disproportionate number (relative to exposure opportunity) involved organophosphate pesticides.

Demographic Diversity. MCS-like illnesses have been reported by industrial workers, individuals exposed in contaminated communities, tight-building occupants, and individuals with personal and unique exposure histories, for example to pesticides in their homes (Table 1). These groups differ greatly in terms of age, sex, social group, and the kinds of medical specialists they consult. What they share in common is a history of a major chemical exposure event and similar kinds of complaints following that event, particularly complaints about symptoms occurring after exposure to common environmental substances that were formerly tolerated. The demographic diversity of these groups suggests that a real problem may be occurring.

Temporal Cohesiveness. The temporal cohesiveness of MCS-like illnesses occurring within a group of individuals sharing a recognized, major chemical exposure (for example, near-simultaneous development of symptoms in several family members, co-workers, or community members exposed to the same chemical or mix of chemicals) helps point to a problem that is real in those circumstances.

TABLE 1. Chemically Sensitive Groups

Group	Nature of Exposure	Demographics
Industrial Workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
Tight-building occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white collar office workers and professionals; 20 to 65 years old; school children
Contaminated communities	Toxic waste sites; aerial pesticide spraying; ground water contamination; air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs, and pesticides	70-80% females; 30-59 years old (Johnson and Rea, 1989); white middle to upper middle class professionals

Source: Ashford and Miller, 1991.

Total Load. An apparent threshold effect, referred to by some as the patient's "total load", has been noted and cited by some practitioners to help explain why an individual develops this syndrome at a particular time. Illness is said to occur when the total load of biologic, chemical, physical, and psychologic stressors exceeds some threshold for the patient. This concept has emerged from clinical observations. No direct experiments have been done to test its validity in humans. However, Hans Selye's work demonstrating the General Adaptation Syndrome in animals exposed to various stressors lends support to this idea (Selye, 1946).

Triggering

Triggering by Extremely Low Levels of Chemicals. Following induction of the illness, patients report subsequent triggering by extremely low levels of exposure to common chemicals, levels that are tolerated by most of the population.

Spreading. Spreading of sensitivities to other, often chemically dissimilar, substances is commonly reported, with each substance triggering a different but reproducible constellation of symptoms.

Characteristic Constellation. For a given patient with a given exposure, a characteristic constellation of symptoms results. Indeed, even when no odor is present, MCS patients may be able to identify the nature of the exposures based solely upon the pattern of symptoms they experience.

Dose dependence. The severity of symptoms is proportional to the "dose" (duration and magnitude) of the exposure in the sensitized individual.

Pronounced Stimulatory and Withdrawal Symptoms. MCS patients sometimes report that when they are exposed to environmental incitants, either foods or chemicals, they may initially experience a stimulated feeling that is either pleasant (euphoria) or unpleasant (jitteriness); this is followed by withdrawal symptoms (headache, irritability, depression, fatigue) when the exposure is reduced or terminated (Ashford and Miller, 1991). Very sensitive individuals report having experienced fewer and shorter-lived stimulatory effects and more pronounced withdrawal symptoms as their illness progressed. In an extreme case, onset of exposure might be associated with manic behavior and withdrawal from the same exposure might be linked to depression.

Inter-Individual Variability. Different MCS patients exposed to the same substance(s) may experience different symptoms and symptom severity.

Intra-Individual Reproducibility. Individual MCS patients report similar symptoms occurring each time a specific exposure is encountered.

Multiple Exposure Routes Trigger Symptoms. Patients' symptoms may be triggered by inhalation, ingestion, mucosal contact, or injection. Eyedrops, dental materials, suppositories, IVs, and other exposures have been reported to elicit symptoms. Exposure to a given substance in a given patient but via different routes has been reported to result in similar symptoms.

Subsensory Triggering. Onset of symptoms may occur with exposure to chemicals at concentrations below the olfactory threshold. For example, patients may report entering a room, experiencing a "reaction", and learning only later that pesticides had been applied recently. Anosmia and chemical sensitivity are not mutually exclusive; a certain number of MCS patients have no sense of smell, but nevertheless report symptoms with exposure.

Rapid Onset of Symptoms. MCS patients frequently report onset of symptoms within a few seconds of being exposed. In addition, the symptoms have an on/off quality. As quickly as symptoms may begin, an almost immediate cessation of symptoms has been reported following neutralization or use of alkali salts. Such responses might suggest rapid shifts of ions across cell membranes, a neurologic or immunologic mechanism, or possibly conditioning.

Variable Threshold for Triggering. Following development of MCS, major exposures, for example, an airplane trip or exposure to pesticides at work, may result in a general decrease in tolerance for chemical substances, even substances for which tolerance may have been regained. Following such exposures, gradual improvement usually occurs, but it may take days, weeks, or even months, depending on the patient and the severity

of the exposure. Patients may say that following a particular exposure, they "lost their foods", meaning they once again lost tolerance for foods they had been able to reintroduce into their diets. This variability in responsiveness in some ways resembles the increased bronchial reactivity that occurs in asthma and increased basophil releasibility in atopic dermatitis following major exposures to incriminated inhalants or foods, respectively.

Decrease in Symptoms with Oral Versus Nasal Inhalation. Some MCS patients have noticed that, faced with an unavoidable exposure (for example, traffic exhaust or perfume in an elevator), inhaling via their mouths instead of their noses mitigates symptoms.

Limited Voluntary Control. Certain patients report that biofeedback, self-hypnosis, or variations on these techniques improve their ability to cope during exposures and lessen symptom severity. Such techniques seem to be less helpful for more severe exposures and symptoms.

Adaptation. Adaptation occurs with frequent or continuous exposure, and acute symptoms may become chronic and no longer appear related to particular exposures. This will be discussed later in more detail. Potentially, adaptation may have enormous significance for future research in this area.

Other Intolerances

Food and Alcohol Intolerances. Food and alcohol intolerances are estimated to occur in a sizeable percentage, perhaps up to 80% (Rea, 1988) of individuals with MCS. Foods are complex mixtures of many chemicals, some of which can also be air contaminants. For example, pinene is a constituent of both bathroom air fresheners and oranges. Many MCS patients first become aware of their intolerance for ingestants when they consume an alcoholic beverage, such as red wine or beer, and become ill afterward.

Drug Intolerances. MCS patients often respond poorly to usual doses of medications and may even report difficulties with excipients, binders, coloring, and flavoring agents. Several physicians have reported that their patients are intolerant of the anticholinergic side-effects of various drugs (Schottenfeld, 1987).

Hyperresponsiveness to Physical Stimuli. Some MCS patients may perceive not only chemical but also physical stimuli, including touch, sound, and light, as greatly magnified. These individuals describe their nerves as being easily irritated, and they experience pain or extreme discomfort when someone bumps their bed or they hear conversational-level noises.

Symptoms/Signs

Multisystem Symptoms. Commonly, this patient group experiences symptoms involving virtually any system in the body and often several systems simultaneously. These do not coincide with other known multisystem disorders, such as an endocrinopathy.

Frequent Central Nervous System (CNS) Complaints. Mood, memory, and concentration difficulties are among the CNS symptoms these patients report most frequently.

Rhinitis. The majority of MCS patients appear to have nasal inflammation or rhinitis, suggesting that inflammatory processes are involved in MCS. Rhino-laryngoscopy, nasal biopsies, and assays of mediators in nasal lavage fluid may provide useful data in the future. Doty (1988) reported greater nasal airway resistance among MCS patients than normal controls, both before and after unblinded exposure to phenyl ethyl alcohol and methyl ethyl ketone. Despite increased nasal airway resistance, Doty's subjects had olfactory thresholds for phenyl ethyl alcohol and methyl ethyl ketone that did not differ significantly from the olfactory thresholds of controls.

Personal/Predisposing Characteristics

Apparent Female Preponderance: Among certain demographic groups in which chemical sensitivities have been reported, a greater number of females than males appear to be affected. Although exposure to domestic chemicals in poorly ventilated homes cannot be discounted as a factor, numerous medical conditions and diseases, such as most connective tissue diseases, show a disproportionate

number of females affected. Because the maternal immune system is challenged with paternal antigens during pregnancy, its immunologic repertoire and responses may somehow make it more vulnerable to chemical exposure. In a Soviet experiment, females were shown to be more susceptible to the effects of low-level organophosphate exposure than their male counterparts (Krasovskii et al.). The incidence of cutaneous drug reactions in females is 35% greater than among males (Bigby et al., 1986).

Food Cravings and Addiction. Patients often report having carbohydrate or other food cravings, being "chocoholics" or addicted to certain foods, such as baked goods, peanuts, popcorn, sugar (especially corn sugar), potatoes, a particular soft drink, etc. Some report sipping coffee, tea, or soda all day long, carrying it with them wherever they go. Intense food cravings following chemical exposures may be reported, for example, an uncontrollable urge to stop and buy candy after driving in heavy traffic.

Pre-Morbid History of Ill-defined Medical Conditions. Diagnoses such as hypothyroidism, chronic fatigue, temporomandibular joint dysfunction, and fibrositis seem to be more prevalent among MCS patients. Simon et al. (1990) reported an average of 6.2 unexplained physical symptoms before workplace exposure among workers who developed "environmental illness", versus 2.9 such symptoms for controls.

Pre-Morbid History of Depression. Simon et al. (1990) also found that 54% of workers who developed chemical sensitivity reported anxiety or depression prior to their workplace exposure, versus 4% of controls. Others corroborated these impressions, although the sources of these patients' depression and anxiety, whether endogenous or chemically-related, have yet to be demonstrated.

Target Organs Vary Over Time. Patients may report lifelong medical problems, but these affect different organ systems over time. For example, they may have experienced colic as babies, asthma in grade school, stomach problems in high school, headaches in college, and finally chronic fatigue and memory and mood difficulties following a major exposure event.

Family History of Chemical Intolerance. Many patients report a family history of chemical intolerance or addiction. The fact that similarly-exposed co-workers or household members of patients often do not develop MCS suggests that MCS patients have a possible genetic, nutritional, psychologic, or other predisposition, or an accumulation of effects from prior exposures.

Laboratory Findings

Lack of a Consistent Immunologic Abnormality. A variety of immunologic tests have been conducted in this patient group including measures of both cellular immunity (especially T and B lymphocyte counts and ratios) and humoral immunity (especially immunoglobulin levels). Some of the most striking data are those of Levin and Byers (1987), which show an apparent decrease in helper/suppressor ratios among various exposed populations compared with controls. By contrast, other investigators claim that immune parameters for these patients generally fall within expected normal ranges (Terr, 1986). Further studies of T and B lymphocytes in these patients, using healthy age- and sex-matched controls, are needed before conclusions can be drawn. In any event, because helper and suppressor T-cell numbers and ratios of patients and controls overlap greatly, one-time measurements of these parameters are of little value for clinical diagnosis.

Increased frequency of Autoimmune Antibodies. A few investigators have reported an increased frequency of low titers of various autoimmune antibodies (ANA, anti-smooth antibody, thyroid antibodies, and others) among individuals who report becoming ill after an identifiable exposure to pesticides, solvents and, more recently, pentachlorophenol (Broughton and Thrasher, 1990; McConnachie and Zahalsky, 1991). One group of researchers has reported that 35 (91%) of 39 individuals with ongoing exposure to trichloroethylene in drinking water had one or more positive results in a panel of autoantibody tests, versus 6 (21%) of 28 controls. Two years after removal from exposure, 41% of the exposure group continued to have one or more positive autoantibody tests, suggesting that avoidance of exposure led to some improvement (Broughton and Thrasher, 1990). The physiologic significance of low titers of autoantibodies is unknown and,

although of considerable research interest, their diagnostic utility is compromised because 20% of healthy controls had similar findings. Such data could suggest an autoimmune response to host proteins altered by reactive environmental chemicals. In future work, careful attention should be directed to employing matched controls and blinded specimens and to assessing inter- and intra-laboratory reproducibility and the day-to-day variation in individual patients' results.

Increased Frequency of Activated T-Lymphocytes. The same laboratories that report an increased frequency of autoimmune antibodies in these patients also report an increased frequency of activated T-lymphocytes (Tal or CD26). If borne out, such a finding might suggest an inappropriate or persistent immune response that fails to clear chemicals from the tissues. Activated T cells have been reported in association with multiple sclerosis, infections, and various other inflammatory states. The significance of activated T-cells in this setting is unknown but merits further study.

EEG Abnormalities. A recent study compares EEGs from 58 "universal reactors", 55 healthy controls, and 89 patients from a psychology practice (Staudenmayer and Selner, 1990). EEGs of universal reactors more closely resembled EEGs of psychologic patients than those of controls. The authors, however, dismissed the environmental hypothesis that psychologic and psychiatric disturbances could be consequences, rather than causes, of MCS (Davidoff et al., 1991). Similar EEG changes with increased beta and decreased alpha activity have been reported among organophosphate-exposed workers (Duffy et al., 1979).

ADAPTATION[1]

Adaptation is also called "acclimation" or "acclimatization", "habituation", or "developing tolerance". "Acclimatization" often refers to the process of workers gradually becoming accustomed to exposures on the job, for example, heat stress. Understanding the possible role of adaptation in MCS is important for two reasons. (1) Adaptation may interfere with discovering effects on the body from a particular exposure, and (2) chemical exposures may adversely impact adaptive mechanisms and thus lead to illness.

That human beings adapt after chronic exposure to environmental challenges is widely recognized for a variety of substances. For example, the first cigarette an individual smokes might result in eye and throat irritation, but, as they continue to smoke, most individuals adapt over time and experience primarily the pleasurable effects of nicotine on the brain. After months or years, more cigarettes may be required for the same amount of lift, and, eventually, smokers may exhibit addictive behaviour, seeking cigarettes more frequently. Subsequent quitting may lead to withdrawal symptoms including irritability, drowsiness, fatigue, moodiness, and headache. The reformed smoker may become extremely intolerant of the smoke of others, even in tiny amounts, and suddenly recall the irritation and unpleasant feelings associated with the first cigarette ever smoked. Over time, the individual had "adapted" to those effects.

Adaptation, which on the surface seems a good thing for the organism, may in fact be a two-edged sword. Tolerance for the noxious properties of exposure may make the individual more comfortable in the exposure and allow other harmful consequences of exposure to continue. Thus, heavy smokers who are "adapted" to tobacco smoke are also at increased risk for developing emphysema, lung cancer, or cardiovascular disease. Parallel analogies are valid for caffeine, alcohol, and other drugs, and frequent exposure may result in adaptation (irritation and other warning signals may disappear), continued exposure may lead to addiction, and reduction or cessation of exposure may precipitate withdrawal symptoms.

Some physicians have observed food and chemical adaptation and addiction in their chemically sensitive patients (Randolph, 1962, 1965). For MCS patients, multiple incitants, not only tobacco smoke, may be involved and, conceivably, all incitants may need be avoided simultaneously for improvement to occur.

Confusion could arise if patients seek physicians' help for withdrawal symptoms when they are no

[1] Modified in part from Ashford, N.A. and Miller, C.S. (1991). Chemical Exposures: Low Levels and High Stakes. Van Nostrand Reinhold, New York.

longer exposed (or less exposed) to the offending agents. For example, irritability may occur when individuals smoke fewer cigarettes than usual, or headaches may develop when they drink less caffeine. Such unpleasant withdrawal symptoms may be forestalled by smoking another cigarette or taking another drink of coffee, thus perpetuating addiction. Because smoking a cigarette or drinking a cup of coffee in the morning (after about 8 hours abstinence) relieves irritability of headache and makes patients feel better, they may not suspect that cigarettes or coffee might also be the source of their difficulties.

Occupational health presents other examples of acclimatization, inurement, or tolerance development, for example, after repeated exposure to ozone, nitroglycerin, or solvents (Ashford and Miller, 1991). The incitants mentioned thus far differ considerably from one another; some are ingestants, other inhalants; and their physical states and chemical composition vary greatly. The human body appears able to adapt to an enormous range of substances.

Ozone had been the focus of considerable research on adaptation. Intrigued by how little respiratory illness and death occurred in very polluted cities that had high levels of ozone and suspecting that adaptation might play a protective role, Hackney and associates (1977a) compared the responses of four Canadians (not adapted) and for Californians (adapted) to ozone challenges. Although individual reactivity varied greatly, the Californians were only minimally reactive to levels that caused coughing, substernal discomfort and airway irritation, pulmonary-function-test decrements, and increased red blood cell fragility for the Canadians.

In another experiment, six volunteers with respiratory hyperreactivity were placed in an environmental chamber with ozone at 0.5 ppm, typical of high ambient levels, for four days (Hackney et al., 1977b). Five of six showed decreased pulmonary function during days 1 to 3, but gradually improved almost to baseline by day 4, suggesting adaptation had occurred. The authors note that not all adverse effects of ozone may be prevented by adaptation; for example, increased red blood cell fragility may persist. Thus, adaptation or masking of some (usually acute or irritant) symptoms may occur while other physiologic alterations continue.

Individuals' abilities to adapt to ozone appear to depend on their initial sensitivity to it. More sensitive persons adapt more slowly and cannot maintain adaptation as long, usually less than seven days after exposure ceases (Horvath et al., 1981). Although adaptation to ozone may be related to what occurs in MCS, chemically sensitive patients frequently blame solvents for their symptoms (Terr, 1989; Cone et al., 1987) and adaptation to solvents has been well-documented. Vapors from various solvents are the most prevalent of indoor air contaminants (Molhave, 1982), and indoor air contaminants are of major concern to MCS patients. The volatile organic compounds associated with sick building syndrome are in large part solvent vapors.

Persons who have painted or used solvents extensively are well aware of the olfactory fatigue (nasal adaptation) that occurs and may have experienced the stimulatory and depressive (withdrawal) effects of solvents. Alcoholic beverages contain the solvent ethanol, which has related and familiar stimulatory and withdrawal effects.

Studies of xylene, one of the most prevalent solvents in indoor air, demonstrate that its effects are attenuated as exposure continues, presumably due to adaptation (Riihimaki and Savolainen, 1980). Riihimaki and Savolainen exposed healthy male volunteers to constant (100 or 200 ppm) and varying (200 or 400 ppm hourly peak) concentrations of xylene, adjusting baseline concentrations in the latter case so that a mean concentration of 100 or 200 ppm was maintained. Exposures occurred over a six-hour period (with a one-hour break at noon) for five days, followed by a two-day weekend without exposure, and one to three more days of active exposure to xylene. The investigators measured a variety of psycho-physiologic parameters, including reaction time, body balance, manual dexterity, and nystagmus.

Most of the adverse effects of xylene on normal subjects "tended to disappear after a few succeeding days of exposure". However, "after the weekend away from exposure, the effects were again discernible". Riihimaki and Savolainen conclude: "This phenomenon suggests that tolerance had

developed over a few days with regard to psychophysiologic effects by xylene".

We have mentioned several exposures that may involve adaptation. Clearly, individuals with or without multiple chemical sensitivities undergo adaptation to a wide variety of substances in their environment. However, the specific role adaptation plays in the dramatic responses patients report with MCS is not clear.

Patients may experience the effects of adaptation and de-adaptation without realizing what has occurred (Ashford and Miller, 1991). For example, a person with asthma may feel well after spending a week on a Caribbean island, breathing relatively uncontaminated air, and eating a diet devoid of usual foods. Then, exhaust emissions from the engine of a boat the individual takes to go home may bring on a severe, life-threatening asthmatic response. Back home in a metropolis, the person readapts, acclimatizes to auto emissions, combustion products and other air pollutants in the area, and experiences only chronic wheezing. Thus, following deadaptation (removal from incitants), the individual exhibits a more acute and convincing reaction upon re-exposure. This is what is reportedly observed when patients are tested in an environmental unit following deadaptation. Some of these reactions are so acute and convincing when they occur in daily life, that patients themselves may erroneously (at least in the eyes of some) surmise they must have an "allergy" to the incitant. Physicians may be skeptical and elect to challenge a patient with a supposed incitant. If, however, the patient is not deadpated or unmasked when tested, no reaction may occur, and the physician will be convinced the "allergy" was all in the patient's mind.

The deadaptation of patients may be critical to the study and the diagnosis of MCS for several reasons.

1. People are often exposed to dozens of potential incitants simultaneously, such as volatile organic compounds in a tight home or building, and literally hundreds over the course of a single day, so that health effects of these exposures may overlap, making it difficult to discern the cause-and-effect relationships (Figure 1).

2. With continuous or frequent exposure to the same substance or chemically-related substances (such as xanthines in coffee, tea, chocolate, and colas), individuals adapt or develop tolerance to certain aspects of those exposures. Acute symptoms may gradually give way to chronic symptoms that may bear no apparent relationship to exposure. Exposures may never stop long enough for the patient to reach a baseline from which responses to challenges can be accurately gauged.

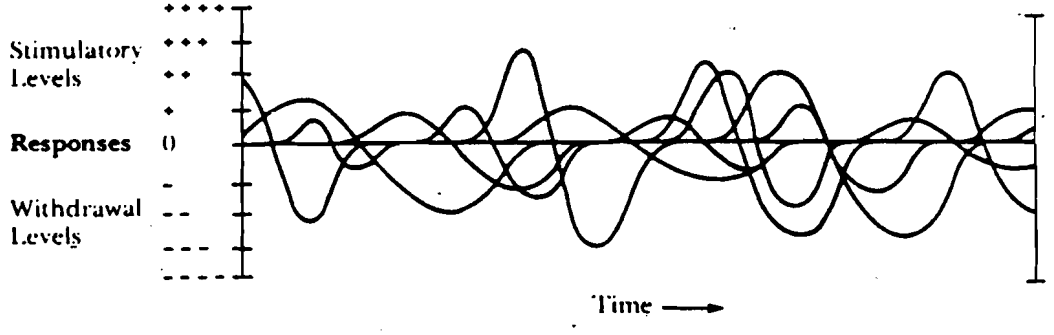


FIGURE 1. Overlapping of responses to food and chemical incitants in an individual with multiple exposures and multiple chemical sensitivities. *Source:* Ashford and Miller, 1991. Reprinted with permission of the publisher.

Graphical Representation of an Individual's Symptoms Before and After Entering an Environmental Unit

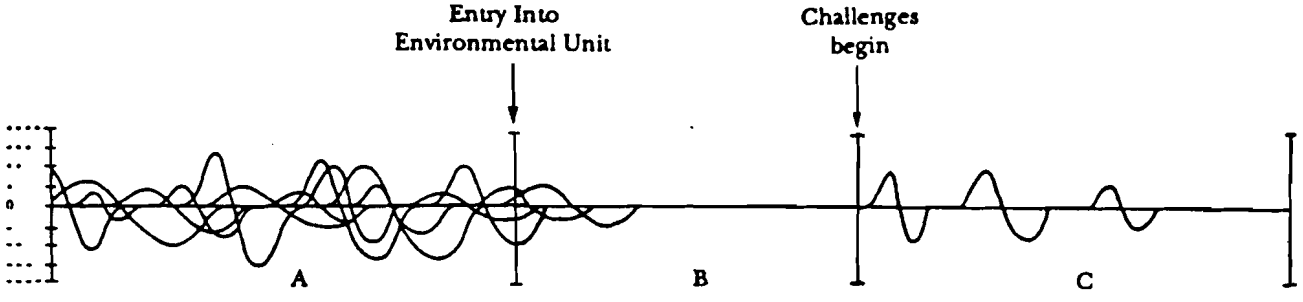


FIGURE 2. In time period A an individual is responding to multiple incitants encountered in normal daily living (chemicals and/or foods), with stimulatory and withdrawal effects that overlap in time. At any particular time, how the person feels is determined not only by ongoing exposures, but by previous exposures whose effects may still be waning. In time period B, the individual enters an environmentally controlled facility, fasting. With cessation of contributory exposures, withdrawal effects occur, for example, headache, fatigue, and myalgias. Symptoms continue for some time (typically 4-7 days) until the individual reaches "0" baseline. In some time period C, single challenges to suspected incitants are administered. Symptoms, often robust, develop soon after challenges, allowing patient and physician to begin to observe the relationship between exposures and symptoms for that individual. *Source:* Ashford and Miller, 1991. Reprinted with permission of the publisher.

Environmental units have been used to help overcome the masking effect of adaptation and the problems of overlapping exposures that result in overlapping responses to multiple agents. Such environmental units may in fact allow backing up or reversal of adaptation. Figure 2 graphically depicts the changes in symptoms that might occur in a patient who enters an environmental unit. Advantages of such an approach over conventional methods for determining toxicity may include facilitating detection of subclinical, prepathologic effects of chemicals and providing more than just a snapshot of an individual's response to substances. Removing a person from interacting, time-dependent stimuli in this way could allow the unraveling of multiple causes. Environmental units are an essential research tool. Many carefully conducted studies of chemical effects with negative or equivocal outcomes may have been flawed by failure to take adaptive mechanisms into account. The potential consequences of such an oversight are major.

Important questions that must be addressed in future studies of chemical sensitivity include:

1) Are subjects in a deadapted state before challenges so that extraneous exposures during and before a challenge (up to several days before) do not interfere with testing?

2) Are open challenges performed first to confirm that the placebo (clean air or a masking odor) is in fact a placebo and that the "active" challenge is something to which the patient has had a demonstrable response?

3) What is the recency and latency of the patient's exposure to the substance being tested? In other words, had enough time elapsed (about a week or so) so that the person is no longer adapted or responding to the last exposure but

not too much time so that sensitivity has waned? Time elapsed since last exposure is recognized as a crucial variable in conducting challenges of patients with, for example, occupational asthma.

Carefully designed studies of deadapted patients in an environmental unit, using double-blind, placebo-controlled challenges, are an essential first step for helping resolve current professional antagonisms and placing this subject on a scientific footing.

POSSIBLE MECHANISMS FOR MCS: THE LIMBIC SYSTEM[2]

The most frequently cited physiologic theories to explain chemical sensitivity involve the nervous system, the immune system, or an interaction between them, because these two systems most clearly link the external environment and the internal milieu. Both can respond to exquisitely low concentrations of chemicals. The rapid responsiveness of these systems also makes them attractive candidates because symptoms of food or chemical sensitivity have been reported to develop with seconds of exposure. Many chemicals, such as polybrominated biphenyls (PBBs) and trichloro-ethylene, affect both the nervous system and the immune system. Until 1980, the idea that direct communication between the nervous and the immune system might occur was widely debated. Subsequently, the existence of a neuroimmuno-endocrine axis has been increasingly realized. Several discoveries have helped to confirm the presence of two-way communication between the nervous and the immune systems (Payan et al., 1986).

Kilburn (1989) proposes the human nervous system, because it is so highly evolved, may be most susceptible to environmental agents:

> "Sensitivity may be its undoing. The intuitive hypothesis is advanced that the nervous system is the most liable of the body's systems to damage from environmental toxins. Appreciation of damage may be masked because subtle dysfunction is concealed by the nervous system's remarkable redundancy and substitution of functions, or it is overlooked in clinical evaluations which are usually only qualitative."

The hypothalamus, which is in close association with the limbic system, has attracted considerable attention because it is the focal point in the brain where the immune, nervous, and endocrine systems interact (Bell, 1982). Bell notes that assuming a direct cause-and-effect relationship would be premature, but that the hypothalamus could mediate food and chemical addictions in patients with multiple chemical sensitivities. The olfactory system has known links to the hypothalamus and other parts of the limbic system, which has led Bell to speculate that "the olfactory system, hypothalamus and limbic system pathways would provide the neural circuitry by which adverse food and chemical reactions could trigger certain neural, psychologic and psychiatric abnormalities". Patients with chemical sensitivities have reported food cravings, binges, violence, or hypersexual activity following chemical exposures. A model involving the hypothalamus could help explain such behavioral changes.

Some authors have alleged that psychologic conditioning to odors is responsible for patients' reactions to chemicals. Of course, odor conditioning could be involved in selected cases. However, physiologic mechanisms involving the limbic system may also occur. A direct pathway from the oropharynx to the brain and the hypothalamic and limbic region has been demonstrated in rats (Kare, 1968; Maller et al., 1967). Substances placed in the oropharynx migrated to the brain in minutes via a pathway other than the blood stream and in higher concentrations than if administered via the gastrointestinal tract, suggesting a direct route from mouth to brain. Similarly, Shipley (1985) showed that inhaled substances that contact the nasal epithelium may cross into the brain and be distributed widely via transneuronal transport. Thus, molecules that are inhaled and contact the olfactory apparatus could conceivably influence functions in other parts of the brain.

Ryan and associates (1988) studied 17 workers who attributed changes in thought processes, particularly memory and concentration difficulties, or changes

[2]Modified in part from Ashford, N.A. and Miller, C.S. (1991). Chemical Exposures: Low Levels and High Stakes. Van Nostrand Reinhold. New York.

in mood, to their exposure to solvents. Workers with "cacosmia" (a heightened sensitivity to odors resembling that reported by chemically sensitive individuals) performed most poorly on neurobehavioral tests requiring verbal learning or visual memory. The authors believed their findings supported a hypothesis that chronic solvent exposure may affect the "rhinencephalic structures" (primitive "smell" brain), the evolutionary precursor of the limbic system.

This phylogenetically ancient part of the brain is present in all mammals. It influences the organism's interaction with its environment in many subtle ways essential for preservation of the individual, its offspring, and the species. Limbus (Latin for "margin" or "rim") refers to its rim-like appearance around the inner edge of the cerebral hemispheres. Figure 3 shows its component parts. Note the close anatomical relationship to the olfactory bulb. The olfactory nerves are the brain's most direct contact with the external environment. No protective blood-brain barrier exists here. Each olfactory nerve consists of bipolar neurons with one end in the upper part of the nose and other in the brain (olfactory bulb). Odors can elicit electrical activity in the amygdala and hippocampal areas of the limbic system via this pathway (Monroe, 1986). Subsensory exposure to chemicals may cause protracted, if not permanent, alterations in the electrical activity of the limbic region, beginning first with the most sensitive structures, particularly that portion of the amygdala that analyzes odors (Bokina et al., 1976). All parts of the limbic system are intimately interconnected. Interestingly, ablation of the olfactory bulb in laboratory animals serves as a model for depression that investigators have used to test the efficacy of various antidepressants (Jesberger and Richardson, 1988).

The amygdala, the most sensitive portion of the brain to chemical stimuli, is involved in feelings and activities related to self-preservation, such as searching for food, feeding, fighting, and self-protection (MacLean, 1986). It has been dubbed "emotion central", signifying its importance in mood

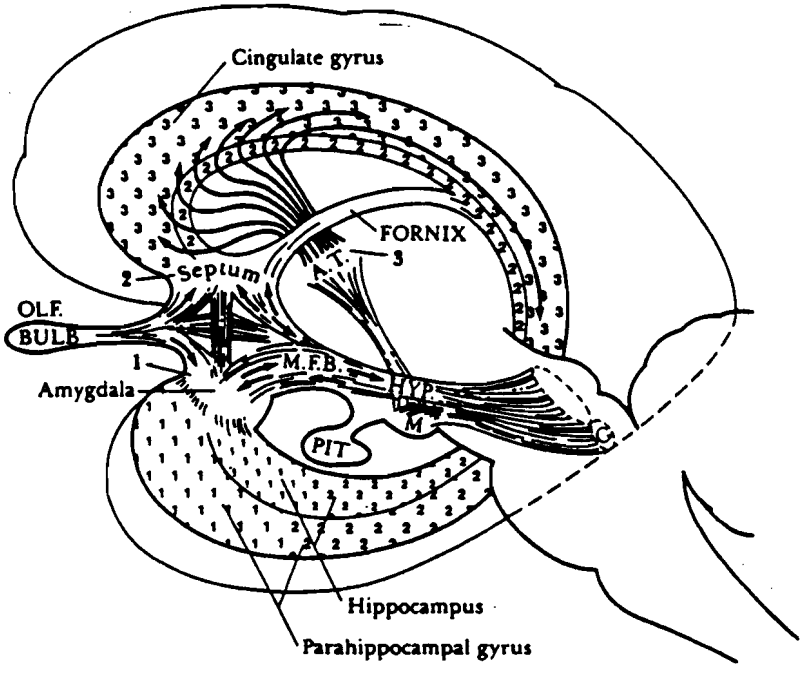


FIGURE 3. Three major subdivisions of the limbic system. The small numerals 1, 2, and 3 overlie, respectively, the amygdaloid, septal, and thalamocingulate divisions. The corresponding large numerals identify connecting nuclei in the amygdala, septum, and anterior thalamus. Abbreviations: AT, anterior thalamic nuclei; G, tegmental nuclei of Gudden; HYP, hypothalamus; M, mamillary bodies; MFB, median forebrain bundle; PIT, pituitary; OLF, olfactory. *Source:* MacLean, 1973. Reprinted with permission of the publisher.

states. The cingulate gyrus appears to influence maternal care and nursing, separation cries between mother and offspring, and playful behavior, including wit and humor (MacLean, 1986), qualities that many MCS patients feel have been impaired. The septum involves feeling and expression relating to procreation. Lesions in the septal area may cause hyperresponsiveness to physical stimuli (such as touching, sounds, or temperature changes), hyperemotionality, loss of motivation, excessive sugar and water intake, and fear of unfamiliar situations (Isaacson, 1982), phenomena reported by some chemically sensitive individuals.

Another limbic region, the hippocampus, appears important for laying down new memories and is thus essential for learning (Gilman and Winans, 1982). Hippocampal lesions may cause difficulty in retaining recent memories (Isaacson, 1982). The hippocampus, at the intersection of numerous neural pathways and in a critical position to affect the transfer of information from one brain region to another, acts as an information switching center. Learning and memory decrements are a frequent consequence of exposure to toxic substances, and some researchers view the hippocampus as a prime target for such toxins (Office of Technology Assessment, 1990; Walsh and Emerich, 1988). Damage to the hippocampus itself, or to nerves leading to or from it, may adversely affect the synthesis, storage, release, or inactivation of the excitatory and inhibitory amino acids that serve as neurotransmitters in this region of the brain. Toxins may disrupt the delicate balance of these amino acids, perhaps leading to the release of a flood of excitatory neurotransmitters that damage neighboring cells, a phenomenon that has been called "excitotoxicity" (Office of Technology Assessment, 1990). Remarkably small perturbations of hippocampal function may have large and long-lasting effects on behavior and cognition (Walsh and Emerich, 1988).

The hypothalamus, which interacts closely with the limbic region, governs (1) body temperature via vasoconctriction, shivering, vasodilation, sweating, fever, and behaviors such as moving to a cooler or warmer environment or putting on or taking off clothing; (2) reproductive physiology and behavior; (3) feeding, drinking, digestive, and metabolic activities, including water balance, addictive eating, and complete refusal of food and water leading to death; (4) aggressive behavior and physical manifestations of emotion such as increased heart rate, elevated blood pressure, dry mouth and gastrointestinal responses (Gilman and Winans, 1982).

The hypothalamus is also the locus at which sympathetic and parasympathetic nervous systems converge. Many symptoms that patients experience with food and chemical sensitivities could be related to the autonomic nervous system. For example, altered smooth muscle tone produces Raynaud's phenomenon, diarrhea, constipation, and other symptoms reported by these individuals. The hypothalamus also appears to influence anaphylaxis and other aspects of immunity (Stein et al., 1981). Conversely, antigens may affect electrical activity in the hypothalamus (Besedovsky et al., 1977).

It is important also to recognize that thoughts arising in the cerebral cortex that have strong emotional overtones may trigger hypothalamic responses and recreate the physical effects associated with intense anger, fear, and other feelings. To implement its effects, the hypothalamus not only has a direct electrical output to the nervous system but also produces its own hormones, many of which stimulate or inhibit the pituitary's production of hormones (Gilman and Winans, 1982).

Most of the neural input to the hypothalamus comes from the nearby limbic and olfactory areas (Isaacson, 1982). Lesions in the limbic region may be associated with irrational fears, feelings of strangeness or unreality, wishing to be alone, and sadness (MacLean, 1967). A feeling of being out of touching with or out of control of one's feelings and thoughts, not unlike that described by many patients with chemical sensitivity, may be perceived. Some patients report feeling "spacey" or that "the camera isn't on" unless they make an enormous effort to focus their attention.

Doane and Livingston (1986) described potential difficulties for patients with limbic dysfunction. "Activity controlled by the limbic system may seem largely irrational and often is not perceived within one's self in ways that are easily understood or communicated in verbal language".

The dynamic involvement of the hypothalamus and limbic system in virtually every aspect of human physiology and behavior makes injury to these structures an intriguing hypothesis to explain the development of chemical sensitivity with its diverse manifestations. Rich neural connections lie between the olfactory system and the limbic and temporal regions of the brain. Surgical or epileptic patients with damage to the limbic or medial temporal regions of the brain may experience persistent alterations in odor perception (for example, an unusual smell that characteristically precedes seizure activity), as well as learning and memory difficulties (Ryan et al., 1988).

Bell (1990) hypothesizes that chemically sensitive patients may have olfactory-limbic-temporal pathways that are more easily "kindled". In other words, a small signal or insult would more readily trigger firing of nerve cells in brain regions where kindling was present. Kindling might be enhanced by genetic endowment, prior environmental exposures, psychologic stress, hormonal variations, nutritional and other factors. Unlike surgical ablation, which destroys a brain area, kindling is a kind of stimulatory lesion (Girgis, 1986). Kindling has previously been described in the context of seizures. The amygdala, for example, which is particularly susceptible to electrical discharge following either electrical (Girgis, 1986) or chemical provocation (Bokina et al., 1976), is subject to long-lasting alteration when strong or repetitive stimuli are administered. Very potent or repeated stimuli, whether electrical or chemical, may permanently augment the tendency for neurons to fire in the presence of future stimuli, even when challenged with much lower levels than those originally involved.

Girgis (1986) reports a decrease in acetylcholinesterase (AChE), an enzyme that breaks down the neurotransmitter acetylcholine in junctions between nerve cells, that parallels the increase in supersensitivity to stimuli. The limbic system is especially rich in AChE, which is strongly bound to the nerve cell membranes and is very stable. The AChE may play a protective role by enzymatically maintaining acetylcholine concentrations at nerve junctions within safe bounds and protecting susceptible cells in the limbic system from developing "bizarre sensitivity" (Girgis, 1986). Interestingly, physicians who see patients with chemical sensitivities have noted that some of the most severe and debilitating exposures for these patients have involved organophosphate pesticides, which inhibit AChE (Ashford and Miller, 1991; Rosenthal and Cameron, 1991) and have reported that these patients may be especially sensitive to the anticholinergic properties of drugs (Schottenfeld, 1987).

Animals primed by high or repeated lower concentrations of various chemicals, such as formaldehyde or ozone, and subsequently re-exposed to low concentrations of the same chemicals showed an increased tendency toward paroxysmal electrical discharge in the amygdala (Bokina et al., 1976). Bokina observed that although the chemicals he used to sensitize the animals were different in terms of their structure and physical and chemical properties, their effects on the limbic system were remarkably similar, paralleling observations in MCS.

Kindling could help explain the apparent loss of adaptive capacity and spreading of sensitivities to chemically unrelated substances reported in multiple chemical sensitivity. Formerly well-tolerated, low-level exposures to, for example, tobacco smoke or perfume might trigger symptoms in individuals whose limbic areas had been kindled by a prior pesticide or solvent exposure.

One intriguing aspect of the limbic system as a possible mechanism for multiple chemical sensitivities is the system's responsiveness to both chemical and cortical stimuli. Therefore, conscious thought processes and emotional states may influence limbic activity just as chemical or physical stimuli can. The former may be under more or less conscious control of the individual, whereas the latter are almost entirely unconscious and automatic. However, conscious efforts that play into the delicate circuitry of the limbic system may be able to alter or suppress concurrent electrical activity evoked by environmental agents. Some patients with chemical sensitivities report being able to "will" their way out of a mild reaction to a food or chemical, and attempt to control their symptoms in this manner. Most patients, however, say such efforts do not work for their most problematic incitants. In fact, the ability to exercise any conscious effort, even that of simply getting away from the exposure, reportedly may be lost

illness: A disorder of imune regulation. In: Workers With Multiple Chemical Sensitivities. (M.R. Cullen, ed). Occup. Med.: State Art Rev. 2(4):669-682.

MACLEAN, P.D. (1967). The brain in relation to empathy and medical education. J. Nerv. Ment. Dis. 144(5):374-382.

MACLEAN, P.D. (1973). "A Triune Concept of the Brain and Behavior." In: The Hincks Memorial Lecture (T. Boag and D. Campbell, eds.). University of Toronto Press, Toronto, Ontario.

MACLEAN, P.D. (1986). Culminating developments in the evolution of the limbic system: The thalamocingulate division. In: Organization and Clinical Disorders. (B.K. Doane and K.E. Livingston, eds). Raven Press, New York. pp. 1-28.

MALLER O., KARE, M.R., WELT, M., and BEHRMAN, H. (1967). Movement of glucose and sodium chloride from the oropharyngeal cavity to the brain. Nature 213(2):713-714.

McCONNACHIE, P.R., and ZAHALSKY, A.C. (1991). Immunological consequences of exposure to pentachlorophenol. Arch. Environ. Health. 46(4):249-253.

MOLHAVE, L.(1982). Indoor air pollution due to organic gases and vapors of solvents in building materials. Environ. Internat. 8:117-127.

MONROE, R.R. (1986). Episodic behavioral disorders and limbic ictus. In: The Limbic System: Functional Organization and Clinical Disorders. (B.K. Doane and K.E. Livingston, eds). Raven Press, New York. pp. 251-266.

NATIONAL FOUNDATION FOR THE CHEMICALLY HYPERSENSITIVE. (1989). Cheers 1:6.

NATIONAL PESTICIDE TELECOMMUNICATIONS NETWORK (NPTN). (1991). Active Ingredients from Possible Chemical Sensitivities. Texas Tech University Health Science Center, Lubbock, TX.

OFFICE OF TECHNOLOGY ASSESSMENT, CONGRESS OF THE UNITED STATES. (1990). Identifying and Controlling Poisons of the Nervous System. United States Government Printing Office, Washington, D.C.

PAYAN, D.G., MCGILLIS, J.P., and GOETZL, E.J. (1986). Neuroimmunology. Adv. Immunol. 39:299-323.

RANDOLPH, T.G. (1962). Human Ecology and Suceptibility to the Chemical Environment. Charles C. Thomas, Springfield, IL.

RANDOLPH, T.G. (1965). Ecologic orientation in medicine: Comprehensive environmental control in diagnosis and therapy. Ann. Allergy 23:7-22.

REA, W.J. (1988). Chemical hypersensitivity and the allergic response. Ear, Nose and Throat. J. 67(1):50-56.

RIIHIMAKI, V. and SAVOLAINEN, H. (1980). Human exposure to m-xylene. Kinetics and acute effects on the central nervous system. Ann. Occup. Hyg. 23:411-432.

ROSENTHAL, N.E. and CAMERON, C.L. (1991). Exaggerated sensitivity to an organophosphate pesticide (letter). Am. J. Psychiatry 148(2):270.

RYAN, C.M., MORROW, L.A., and HODGESON, M. (1988). Cacosmia and neurobehavioral dysfunction associated with occupational exposure to mixtures of organic solvents. Am. J. Psychiatry 145(11):1442-1445.

SCHOTTENFELD, R. (1987). Workers with multiple chemical sensitivities: A psychiatric approach to diagnosis and treatment. In: Workers with Multiple Chemical Sensitivities. (M.R. Cullen, ed.). Occup. Med.: State Art Rev. 2(4):739-754.

SELYE, H. (1946). The general adaptation syndrome and the diseases of adaptation. J. Allergy. 17:231-247, 289-323, 358-398.

SHIPLEY, M., (1985). Transport of molecules from nose to brain: Transneuronal antegrade and retrograde labeling in the rat olfactory system by wheat germ agglutinin-horseradish peroxidase applied to nasal epithelium. Brain Res. Bull. 15:129-142.

SILVER, W.L. and MARUNIAK, J.A. (1981). Trigeminal chemoreception in the nasal and oral cavities. Chemical Senses 6(4):295-305.

SIMON, G.E., KATON, W.J., and SPARKS, P.J. (1990). Allergic to life: Psychological factors in environmental illness. Am. J. Psychiatry 147:901-906.

STAUDENMAYER, H. and SELNER, J.C. (1990). Neuropsychology during relaxation in generalized, universal 'allergic' reactivity to the environment: A comparison study. J. Psychosom. Res. 34(3):259-270.

STEIN, M., KELLER, S., and SCHLEIFER, S. (1981). The hypothalamus and the immune

response. In: Brain, Behavior and Bodily Disease. (H. Weiner, M.A. Hofer, and A.J. Stunkard, eds). Raven Press, New York. pp. 45-65.

TERR, A.I. (1986). Environmental illness: A clinical review of 50 cases. Arch. Intern. Med. 146:145-149.

TERR, A.I. (1989). Clinical ecology in the workplace. J. Occup. Med. 31(3):257-261.

WALSH, T.J. and EMERICH, D.F. (1988). The hippocampus as a common target of neurotoxic agents. Toxicol. 49:137-140.

DISCRIMINATING BETWEEN CHEMICAL SENSITIVITIES AND AFFECTIVE DISORDERS

Iris R. Bell, M.D. Ph.D.

Department of Psychiatry,
University of Arizona

Invited presentation at the Workshop on Multiple Chemical Sensitivities and their Relevance to Psychiatric Disorders; Health and Welfare Canada, Mental Health Division, Health Services and Promotion Branch and Laboratory Centre for Disease Control, Health Protection Branch; Ottawa, Ontario; December 7, 1992.

Correspondence: Iris R. Bell, M.D. Ph. D., Department of Psychiatry, University of Arizona Health Sciences Center, 1501 North Campbell Avenue, Tucson, AZ 85724 USA.

DISCRIMINATING BETWEEN CHEMICAL SENSITIVITIES AND AFFECTIVE DISORDERS

Iris R. Bell, M.D. Ph.D.

Department of Psychiatry, University of Arizona

Introduction

The purpose of this paper is (a) to review the evidence psychiatric disorders, especially affective disorders, in multiple chemical sensitivity (MCS); (b) provide an overview of the time-dependent sensitization (TDS)/kindling models for recurrent affective disorders and for multiple chemical sensitivity (MCS); and (c) to discuss approaches for discriminating between MCS and affective disorders. For this discussion, MCS is operationally defined as chronic, polysymptomatic syndromes with cognitive, affective, and/or somatic features, evoked in various settings by exposure to low levels of multiple, chemically-unrelated environmental substances (1). The controversy concerning the etiology of MCS derives in part from the argument of proponents that mainly chemical or biological factors cause the problem versus the view of skeptics that mainly psychogenic factors account for the clinical picture (2). The inability to find objective measures to date that are reliably present in the majority of MCS patients has further complicated this issue. In specific, wide variability in immune findings has raised doubt about a consistent role for the immune system as a mechanism for symptom production.

Various investigators have reported increased prevalence of certain psychiatric diagnoses in MCS patient samples. Black et al (3), for example, noted 39% affective disorder (major depression and dysthymia) vs. 13% in age- and sex-matched controls, 4% drug abuse vs. 9% in controls, 43% anxiety disorders (panic/agoraphobia, generalized anxiety, simple phobia, social phobia, obsessive-compulsive disorder) vs. 17% in controls, 17% somatization disorder vs. 0% in controls (n = 23 MCS, n = 46 controls). Overall his group observed 65% MCS patients vs. 28% of controls with any mood, anxiety, or somatoform disorder. Simon et al (4) reported higher scores on scales measuring depression, anxiety, personality disturbance, somatization, and symptom amplification in MCS versus nonMCS workers; they also found greater past but not present anxiety or depressive disorder by history in the MCS individuals (n= 13 MCS; n=23 nonMCS). Similarly, Stewart and Raskin (5) had earlier seen 17% affective disorders, 22% anxiety disorders, 39% somatoform disorders, 17% schizophrenic disorders, and 6% antisocial personality disorder in a series of MCS patients (n= 18), with no controls. Doty et al (6) recorded normal, but significantly higher Beck Depression Inventory scores in a group of MCS patients prescreened to eliminate persons with prior psychiatric histories (6.9 vs. 2.4 in controls; normal is 0-9). Within the occupational medicine literature, some investigators (7,8) have suggested that MCS-like syndromes represent atypical variants of post-traumatic stress disorder. Morrow et al (7), for example, found an overlap in MMPI personality profiles between those of chronically solvent-exposed workers - even those without a toxic spill overexposure event in their histories - and those of war veterans (elevations on Hypochondriasis, Depression, Hysteria, and Schizophrenia/mental confusion). These profiles were distinct from those of chronically medically ill patients. In another group of MCS patients screened for obvious prior psychiatric illness (n = 11), Fiedler et al (9) reported MMPI profiles consistent with somatoform disorder (elevations on Hypochondriasis and Hysteria).

Given this body of data suggesting psychological/ psychiatric symptomatology in MCS patients, some have concluded that psychiatric illness, combined with misattribution of causality to chemicals and/or classically conditioned symptomatology, can explain the seemingly unexplained syndromes of MCS patients. Even from a psychiatric point of view, however, the possibilities are more numerous and complex (2). First, only a subset of MCS patients have evidence of past or present psychiatric disorders, many of which might apply to a large

subset of chronically ill individuals in general. Second, psychiatric diagnoses are simply labels for patterns of symptoms, not etiological explanations in themselves. Third, only a correlation between psychiatric disorders and MCS, not causality, has been shown in the above studies. Logically, it is unestablished whether or not (a) psychiatric disorders cause MCS; (b) MCS causes psychiatric disorders; (c) some third factor causes both disorders and MCS in susceptible persons; or (d) both psychiatric disorders and MCS tend to occur in some of the same people, but have no cause-effect relationship to each other. For instance, according to a recent monograph published by the U.S. National Institute of Mental Health (10), within the field of psychiatry, somatization disorder has no known cause or effective treatment; providing such a label for certain MCS patients therefore adds relatively little to our understanding of the problem. Fourth, some MCS patients have cognitive deficits (9, 11-19) and perhaps neuroimaging blood flow patterns (12,13) different from those commonly associated with depression or anxiety. Fifth, standard of practice in psychiatry dictates that possible organic, i.e. medical and/or pharmacological, causes of the psychiatric symptoms be evaluated, including low thyroid, high cortisol, and other hormone alterations, partial complex seizures (temporal lobe epilepsy), neurodegenerative diseases, autoimmune diseases, tumors, infections, vitamin deficiencies such as low folate, drugs such as alcohol, sedative-hypnotics, antihypertensives, digoxin, cimetidine, and many others (20). Environmental chemicals constitute a possible organic factor in that various pesticides and solvents can cause depression, anxiety, and/or other "psychiatric"-like symptoms on a toxic basis (21).

Time-Dependent Sensitization and Low Dose Reactivity

The usual reply of skeptics to the latter point is that the doses implicated in MCS are far below those of classical toxicology. On the other hand, these low doses are completely within range for a well-established pharmacological process known as time-dependent sensitization (TDS)(22-37). TDS is the ability of a stimulus foreign or novel to the individual to induce progressive amplification of the endogenous response via the passage of time between successive exposures (22). The most extreme form of TDS is limbic kindling, in which repeated electrical or chemical stimuli that have no initial effect on the brain eventually induce full tonic-clonic seizures in lower animals; kindling is an animal model for temporal lobe epilepsy in humans (2,25,36). Pesticides of various classes are among many different agents that can kindle the limbic system (38-42). The properties of TDS are remarkably parallel to the clinical phenomenology of MCS. They include: (a) low doses can bring out a sensitized response better than higher doses (43); (b) multiple, chemically unrelated agents can all induce sensitization (e.g. ethanol, diazepam, cocaine, amphetamine, amitriptyline, haloperidol, enkephalin, beta-endorphin)(22); (c) a single intense exposure or multiple intermittent less intense exposures can activate TDS (22,29,43); (d) individuals differ in susceptibility to sensitization on the basis of genetic traits (28,35) and of inherent hyperreactivity to novelty (43); (e) females are more vulnerable to sensitization than are males (27,34); (f) nonpharmacological and pharmacological stimuli can cross-sensitize with one another (29-31); (g) testing for sensitization in a single session, especially one in a novel setting, may fail to elicit the presence of a sensitized response that actually exists, whereas a series of repeated exposures in the same setting will demonstrate the sensitization (43); (h) the manifestations of sensitization include alterations of behavioral, neurochemical, endocrine, and/or immune variables (2,22); (i) the direction of change in a sensitized response can be either an increase or a decrease in the target variable, dependent on the recent history of all stimuli to which the individual has been exposed (29). It is striking that most of the research on TDS has been in animals, for whom suggestion and expectation effects would be minimal, yet the data overlap the clinical features of MCS patients (1). Thus, the animal model for MCS already exists; it merely requires a change from the use of pharmacological chemicals (drugs) to the use of environmental chemicals. Ethanol (29), a solvent, and sarin (44), an organophosphate pesticide, have already been shown to cause TDS; multiple pesticides have already been shown to cause limbic kindling (39). The hypothesis that MCS is a clinical form of TDS (2) implies that certain experimental designs will be more likely to demonstrate chemical sensitivities, and other designs will lead to missing a real effect (Type II error). *Thus, adverse reactions*

could result from either a single toxic exogenous exposure level or from an endogenously amplified response to repeated, non toxic exposure levels.

Cacosmia and Cognitive Disturbances

Several large scale surveys on over 1300 persons in our laboratory (14-16) have revealed that cacosmia, the subjective experience of altered sense of smell and illness from chemical odors, is distinct from depression and anxiety in the normal population of young and older adults. That is, in our studies, whereas depression or anxiety accounts for a significant portion of the variance in total symptom ratings, affective symptoms do not explain any of the variance in total chemical sensitivity ratings (i.e. cacosmia score). The majority of young adult college students and older adults living in the community report illness from at least one of five environmental chemicals (pesticide, car exhaust, paint, perfume, new carpet); roughly 15% report cacosmia from 4-5 of the five chemicals. Moreover, even though depression or anxiety are controlled for as significant covariates in many analyses, ratings for symptoms such as indigestion, headache, memory trouble or difficulty concentrating remain significantly higher in cacosmics than in noncacosmics. In older adults, we have found that depression explains a large portion of the variance in immediate verbal memory (a problem typical in depressive disorders), but none of the variance in delayed verbal or recognition memory (problems typical of irreversible dementias such as Alzheimer's disease). Instead, cacosmia ratings and objective olfactory sensory identification ability account for a large portion of the variance in the latter memory functions. These findings suggest that cacosmia has a closer relationship to the memory disturbance of irreversible dementia than to that of depression in the elderly. Ryan et al (19) have also noted that cacosmia accounted for a significant portion of the variance in a verbal learning task and immediate visual memory in solvent-exposed workers; even though the workers had greater depression, the depression was not well-correlated with the cognitive deficits. In other words, the symptoms of cacosmics overlap those of affective disturbance only in part, and are not necessarily identical with them.

The reason for the overlap may be explained by several factors. Olfactory stimuli gain access to the brain via the limbic nervous system, a network of brain pathways involved in the regulation of mood, social behavior, appetitive behaviors, learning and memory, endocrine, immune, and autonomic responses (2,45). Researchers have demonstrated that even in normal people, low levels of chemicals such as a perfume constituent that are not consciously detectable, nonetheless cause changes in brain electrical activity on the electroencephalogram (EEG) and interfere with performance on cognitive tasks (46-48). The brain wave changes (e.g. increased beta frequency power) are seen not only in anxiety or arousal, but also in normal humans given acute undetected olfactory stimuli (46-48), monkeys given an organophosphate pesticide on a time-dependent sensitization schedule (44), in chronically solvent-exposed workers (49), and in the nonalcoholic sons of alcoholics given ethanol (50). Kindling of the amygdala, the first way-station from the olfactory system into the rest of the brain, results in increased avoidant and fearful behaviors in response to novelty, even in previously aggressive animals (45); amygdala kindling also produces heightened sensitivity to seizures from opiate drugs (51) and to opioid-dependent reductions in forebrain metabolism (52). Kindling of the hippocampus, a limbic structure, results in disruption of spatial memory function (53). The hippocampus is a key site of neuronal loss in the most common irreversible dementia, i.e. Alzheimer's disease, a disorder which frequently follows or accompanies late-onset major depression in older adults (20). Recent data indicate that late onset depression is biologically more similar to dementia than to early onset depression (more cerebral atrophy on CT scans; higher platelet monoamine oxidase activity)(54,55) and that recurrent depression with its characteristically reversible type of cognitive problems in later life often ends in the development of irreversible dementia (56,57). Thus, even in mainstream psychiatry, identification of depression in a patient not only does not rule out, but may herald the development of a neurological disorder such as dementia (20,21,56).

Links Between Sensitization-Kindling and Psychiatric Disorders Implicated in MCS

The psychiatric and somatic illnesses associated with MCS and cacosmia converge on possible mediation by kindling and TDS, triggered in part by endogenous opioid peptides in the brain (2). Notably, kindling and sensitization are the leading models for recurrent affective disorder in biological psychiatry (36). Post has written extensively on the phenomenological parallels (26,36). He observes, for example, that clear cut psychosocial stressors are more obvious triggers of acute depressive (or manic) episodes early in the course of affective illness, but that life stress plays a progressively smaller role in subsequent recurrences. Later depressions (or manias) occur with little concomitant life stress, as though the brain had learned how to become depressed (or manic) simply by having undergone previous episodes (i.e., sensitized or kindled)(36). In addition, most of the animal models for depression, such as olfactory bulbectomy, catecholamine depletion, and acetylcholine elevation, are capable of accelerating the acquisition of amygdala kindling (58). Olfactory bulb is a site of solvent accumulation in animals (59).

When Dager et al (60) observed solvent-induced new onset panic disorder in certain workers, they suggested that limbic kindling could underlie the etiology of this anxiety disorder, similar to new-onset, drug-induced panic disorder in cocaine abusers. Furthermore, Antelman (22) has proposed that time-dependent sensitization is an appropriate parallel for post-traumatic stress disorder (PTSD), in that an emotionally traumatic event initiates the illness, but minor stressors later reactivate somatic and behavioral hyperreactivity. War veteran PTSD patients experience an opioid-dependent analgesia when viewing war films not seen in non PTSD veterans (61). Opioids can kindle or sensitize the limbic system (25,30).

Somatization disorder (SD), a chronic polysymptomatic illness primarily of women, is characterized both by concomitant histories of major depression, mania, and panic disorder and by high rates of childhood sexual abuse in many women. However, the somatic illnesses of SD women point back to kindling-sensitization and opioids as well. Somatization disorder women have inordinately higher rates of ovarian cysts and irritable bowel than do women with other psychiatric disorders (62,63). Women with polycystic ovary disease are prone to increased prevalence not only of somatoform disorder, but also of temporal lobe epilepsy (cf., kindling)(64-66). Polycystic ovary disease involves in part dysregulation of beta-endorphin control in reproductive hormone secretion (67-70). A leading animal model for irritable bowel showed that corticotropin-releasing hormone (CRH) can reproduce the effects of stress on bowel function (71); CRH has been demonstrated in other studies to kindle the amygdala on a single exposure and facilitate kindling by other stimuli on repeated exposures (72). CRH leads to the release of the cortisol-releasing hormone ACTH as well as beta-endorphin from the same precursor molecule (73). In our laboratory, we have found increased rates of irritable bowel, premenstrual syndrome, and migraine headache diagnoses in highly cacosmic people (14-16). PMS and migraine are both characterized in part by decreases in beta-endorphin levels; in PMS, even the central nervous system response to opioid-blocking drugs fails to produce a homeostatic hormonal response (74-76). We have therefore proposed that one pathway into MCS and cacosmia may involve intermittent rises and falls of endogenous opioid levels, resulting in kindling or sensitization of limbic pathways (Bell et al submitted for publication). Women normally undergo such cycling of endorphins on a monthly basis; additionally, estradiol accelerates the acquisition of TDS (34). Peripheral opioids in general can also induce nonantigenic mast cell release of histamine, an effect that might mediate some somatic, allergic-like manifestations of MCS (77,78).

An essential quality of TDS is that life stress and pharmacological stimuli can activate the same sensitization process (22). Nonpharmacological stress accelerates kindling in animals (79). TDS can have classically conditioned components; heightened responses to a repeated stimulus occur most strongly if the test exposure is given in the same environment in which the sensitization occurred (33). At the same time, it is possible to vary the site of administration of sensitizing stimuli, and the TDS can occur independent of conditioned stimuli (43). Thus, if TDS underlies MCS it is likely that

psychosocial factors, chemical factors, or both could play a role in initiating and/or in perpetuating illness in a given individual, as Black et al's (3) data indicate. However, finding one class of factor cannot rule out a role for the other class of factor (2). This means that either traumatic sexual abuse in childhood or monthly pesticide treatment of one's home in adulthood could set off chronic illness; both psychological and chemical causes could contribute to triggering symptoms. Both would work via the biological changes in brain function they induced in the limbic system, and a life stressor could induce a *biological* sensitivity to low levels of chemicals, certain foods, and drugs later in life by cross-sensitization (2). Studies of TDS show that the process depends in part on the activation of a proto-oncogene, c-fos, as well as on participation of excitatory amino acids in the brain (80). Blocking receptors for N-methyl-D-aspartate (NMDA) with an excitatory amino acid antagonist drug, for example, will prevent both kindled seizures (81) and TDS (80) and interfere with memory formation (82-83), regardless of initiating event or stimulus. **Therefore, regardless of whether the trigger is psychosocial or chemical in nature, the common mediating pathway is biological in the brain (2).** TDS-related cacosmia may reflect dysregulation of the learning and memory processes of limbic neurons (Table 1).

Discriminating between MCS and Affective Disorders: Neuropsychological and Neurological Findings

Thus, the problem of differentiating MCS from affective disorders is complex but soluble, in part by drawing on clinical approaches in neuropsychiatry and neurology (Table 2). Newly emerging evidence in MCS may assist in the task. A simple approach within research studies is to quantify cacosmia, depression, anxiety, and somatic symptoms by questionnaire ratings (14-16). For group analyses, it is a simple matter to use analysis of covariance or multiple regression statistical techniques to determine whether or not the affective ratings account for all, only some, or none of the differences from normals in cacosmia scores, somatic symptom ratings, and/or objective physiological measures such as brain blood flow differences, EEG beta activity (84), cognitive deficits, increased nasal resistance, or increased respiratory rate of MCS patients. Both in clinical and research settings, systematic neuropsychological testing for cognitive deficits and neuroimaging studies such as PET (positron emission tomography) or SPECT (single photon emission tomography) may reveal patterns different from those of "ordinary" psychiatric patients with only depression, anxiety, or somatoform disorders. For example, MCS patients may show more than the effort related poorer performance on attention and concentration tasks seen in depression; instead, MCS patients may also exhibit a more pervasive set of cognitive problems including more severe impairments of delayed and recognition verbal and visual memory; word-finding (naming) abnormalities; constructional deficits; visuomotor coordination and balance problems not seen in depressed patients. In view of the baseline intelligence of many white collar workers who develop MCS (1), ceiling effects may obscure finding abnormalities on certain routine cognitive tests. As a result, additional neuropsychological test strategies may be necessary, such as use of timed tests and/or more difficult tasks, to demonstrate deficits. It is also possible to select MCS patients who are not depressed for comparison with those who are affectively disturbed, especially for neuroimaging studies. Depressed patients often show mainly bilateral reductions in frontal blood flow and metabolism on SPECT and PET scans. Clinical observers in MCS have reported not only the latter findings, but also marked asymmetries in blood flow, changes in temporal lobe (closely linked with hippocampus and memory), and small scattered lesions in multiple sites, a pattern more similar to that of cocaine abusers than of depressives.

Interestingly, some MCS patients also have blood flow abnormalities of the basal ganglia, a region that has been implicated in time-dependent sensitization. Cologne and ammonia cause increased, dopamine-dependent activity in the striatal portion of the basal ganglia on a single exposure (85). TDS induced by repeated drug exposures causes a progressive increase in the release of dopamine in the striatum (86). In view of the clinical data linking hypothyroidism with MCS, the fact that thyrotropin releasing hormone (TRH) receptor binding sites are down-regulated during drug-induced TDS (87) may be significant.

TRH has antiseizure properties and serves as a peptide neuromodulator of dopaminergic function in the brain.

Notably, another neurodegenerative disorder, associated with loss of dopaminergic innervation of the basal ganglia, i.e., Parkinson's disease, is characterized by movement disorder, depressed mood (40% of patients) with lower metabolism in caudate and orbitofrontal cortex on PET scan, and a frontal-subcortical dementia picture (30-40% of patients) (88). In fact, past history of depression is a risk factor for affective disorder after onset of Parkinsonian symptoms; and those Parkinson's patients with postural instability and gait disturbance have more depression than those with tremor (88)(cf., balance abnormalities in MCS patients). Epidemiological studies have linked previous occupational exposures to herbicides and pesticides to risk for Parkinson's disease (89); and xenobiotic metabolism of sulfur-containing compounds is impaired in both Parkinson's and Alzheimer's diseases (90). Even so, the neuropsychological deficits of Parkinson's disease and of other frontal lobe or subcortical lesions overlap those of depression (88); consequently, (a) the severity of deficits (less in depression alone) in the context of (b) the full clinical picture, including gait and balance abnormalities, may be the best guide to differentiating the dementia of depression from dementia due to specific organic dysfunctions. Speculatively, it may be valuable to investigate the prevalence of Parkinson's disease in the family histories of MCS patients for possible neurobiological and mechanistic links between these disorders. In addition to the association with herbicides, at least one other environmental chemical can induce Parkinson's disease; the chemical MPTP (1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine) causes clinical Parkinson's in drug abusers (91). Mixed cases of Parkinson's and Alzheimer's diseases are also noted among the irreversible dementias. Similarly, the findings of both frontal-subcortical (cf., Parkinson's/ concentration, set-shifting deficits, effort-demanding memory) and temporal (cf., Alzheimer's/delayed and recognition visual and verbal memory deficits) blood flow and cognitive abnormalities, albeit reversible, suggest variably mixed subcortical and cortical involvement in MCS patients.

In other words, as in other neuropsychiatric disorders, it is possible that baseline tests of neurophysiological function such as neuropsychological test batteries and neuroimaging studies will constitute the first useful objective measures to differentiate MCS from affective disorders. Moreover, the TDS model provides clear guidance for the proper design of studies to test for individual vulnerability to sensitization as opposed to tests for specific chemical sensitivities. That is, patients must be studied over multiple separate sessions spaced in time (ideally 7-10 days apart) for a progressive increase in responses to double-blind stimuli. One session studies that rely on past history of reactivity to a chemical and then fail to find adverse effects of chemical challenges reflect an improper and inadequate experimental design for MCS testing. Unlike the irreversible neurodegenerative dementias, MCS appears to have a largely reversible quality that offers hope for eventual clinical treatments, but which can confound research efforts to demonstrate its existence. *As a result, it is necessary to look for the sensitizability of the individual over time to a test chemical that is repeatedly given under controlled conditions rather than for acute reactivity to a specific chemical that is only presumed reactive by history.* This approach may enable us to test MCS patients outside an environmental control unit, at least for screening purposes. An important prediction from the TDS-kindling model is that repeated, intermittent retests for ability to sensitize to a given environmental chemical will be much more likely to demonstrate a truly amplified reactivity to chemicals, if present, than will a single test session. Sensitization depends on intermittent exposures to a stimulus; in contrast, tolerance depends on continuous exposure to a stimulus (24) (Figure 1). Both processes can occur to varying degrees at the same time in an individual, and tolerance may obscure the presence of sensitization. The use of unmasking by comprehensive chemical avoidance in an environmental control unit (ECU) will assist in determination of presence or absence of *pre-established sensitivities to specific substances* on subsequent challenge. However, the use of repeated intermittent challenges to the same, initially novel substance (in or out of an ECU) should permit identification of *sensitizable people*, if individually relevant outcome measures are utilized.

As Schwartz et al (92-94) have shown that actual olfactory stimuli produce characteristic changes in topographic EEG responses (with or without conscious awareness of smelling a chemical) that differ from those with placebo stimuli (with a belief in smelling a chemical), double-blinding of low level chemicals is possible. These data suggest that expectation or belief alone is not sufficient to produce the same EEG changes, even acutely, as do true chemicals, in normals. Furthermore, beta activity is the best indicator of brain registration of olfactory stimuli in normals. Topographic EEG (quantitative brain mapping; computerized spectral analysis), while anatomically less precise than PET or SPECT, can provide lower cost, noninvasive, real time-linked objective measures of brain responses to olfactory stimuli. For both clinical and research purposes, standards of topographic EEG responses to consciously undetected olfactory stimuli can be developed for both MCS and depression. Depression may also serve to accelerate sensitization to chemicals. Several studies have previously shown that depression is associated with higher rates of allergies, although allergies are not linked with higher rates of depression (95). Notably, inability to regulate cortisol output is a characteristic of at least half of the major depressions, especially later in life; and increased glucocorticoids accelerate acquisition of TDS (32). Consequently, the endocrinology of depression may serve to facilitate the development of nonatopic chemical sensitivities.

Conclusions

Overall, these sensitive measures of nervous system function and dysfunction, neuropsychological tests, PET/SPECT scans, and topographic EEG, together with measurement over time of cortisol and opioid levels in body fluids, may guide us to a resolution of a previously heated but stalled debate over the nature of MCS. The working hypothesis is: MCS is in part time-dependent sensitization by xenobiotics of the physiological stress response (including but not limited to corticotropin releasing hormone, beta endorphin/enkephalins, cortisol; CNS TRH and dopaminergic activity), involving the olfactory-limbic system and related neural pathways (2). The manifestations of TDS in the limbic system include homeostatic disruption of cognitive, affective, and somatic systems. *Finally, as reviewed above, the finding of psychiatric diagnoses in some MCS patients, supports a sensitization-kindling model for MCS (26,36).* In their own literature, psychiatric researchers themselves consider the essential characteristics of recurrent major depression, bipolar disorder, panic disorder, somatization disorder, and post-traumatic stress disorder (96) to be similar to those of sensitization-kindling (22,26,36,62,63). Even certain carbohydrate and fatty foods, by releasing endogenous opioids in the brain, would be capable of cross-sensitizing to chemicals and stressful life events in a TDS process (97-106). Thus, rather than proving a purely "psychogenic" etiology for MCS, the available psychiatric and neurobiological data point to the likelihood that low levels of environmental chemicals, with or without concomitant psychosocial stressors, can trigger biological dysfunctions within the central nervous system. From a TDS perspective (22,23), psychological factors could play an initiating, perpetuating, or synergizing role in some cases (106); in other cases, chemicals alone could be the primary triggers of CNS/neurological dysfunctions (2,80,86,107-113).

References

1. Ashford NA, Miller CS. Chemical Exposures. Low Levels and High Stakes. NY: Van Nostrand Reinhold, 1991.

2. Bell IR, Miller CS, Schwartz GE. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationship to kindling and affective spectrum disorders. Biol Psychiatry 1992; 32:218-242.

3. Black DW, Rathe A, Goldstein RB. Environmental illness. A controlled study of 26 subjects with '20th century disease.' JAMA 1990; 264:3166-3170.

4. Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. Am J Psychiatry 1990; 147:901-906.

5. Stewart DE, Raskin J. Psychiatric assessment of patients with 20th century disease (total allergy syndrome). Can Med Assoc J 1985; 133:1001-1006.

6. Doty RL, Deems DA, Frye RE, Pelberg R, Shapiro A. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. Arch Otolaryngol Head Neck Surg 1988; 114:1422-1427.

7. Morrow LA, Ryan CM, Goldstein G, Hodgson MJ. A distinct pattern of personality disturbance following exposure to mixtures of organic solvents. J Occupat Med 1989; 31:743-746.

8. Schottenfeld RS, Cullen MR. Occupation-induced posttraumatic stress disorders. Am J Psychiatry 1985; 142:198-202.

9. Fiedler N, Maccia C, Kipen H. Evaluation of chemically sensitive patients. J Occupat Med 1992; 34: 529-538.

10. Smith GR. Somatization disorder in the medical setting (monograph). Rockville, MD: National Institute of Mental Health, 1990.

11. Kipen HM, Fiedler N. Psychological and immunological evaluation of patients with multiple chemical sensitivities. Presented at the 119th Annual Meeting of the American Public Health Association, Atlanta, Georgia, 1991.

12. Callender TJ. Metabolic brain imaging abnormalities in chemically exposed individuals who developed multiple chemical sensitivity syndrome or chronic fatigue syndrome. Presented at the 119th Annual Meeting of the American Public Health Association, Atlanta, Georgia, 1991.

13. Morrow LA, Callender TJ, Lottenberg S, Buchsbaum MS, Hodgson MJ, Robin N. PET and neurobehavioral evidence of tetrabromine encephalopathy. J Neuropsychiatry Clin Neurosci 1991; 2:431-435.

14. Bell IR, Schwartz GE, Peterson JM, Amend D. Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. Arch Environ Health 1992; in press.

15. Bell IR, Schwartz GE, Peterson JM, Amend D. Symptom and personality profiles of young adults from a nonclinical population with self-reported illness from foods and chemicals. Submitted for publication 1992.

16. Bell IR, Schwartz GE, Peterson JM, Amend D, Stini WA. Possible time-dependent sensitization to xenobiotics: self-reported illness from chemical odors, foods, and opiate drugs in an older adult population. Submitted for publication.

18. Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K. Chronic central nervous system effects of acute organophosphate pesticide intoxication. Lancet 1991; 338:223-227.

19. Ryan CM, Morrow LA, Hodgson M. Cacosmia and neurobehavioral dysfunction associated with occupational exposure to mixtures of organic solvents. Am J Psychiatry 1988; 145:1442-1445.

20. Sadavoy J, Lazarus LW, Jarvik LF. Comprehensive review of geriatric psychiatry. Washington, DC: American Psychiatric Press, 1991.

21. Yudofsky SC, Hales RE. Textbook of neuropsychiatry. Washington, DC: American Psychiatric Press, 1992.

22. Antelman SM. Time-dependent sensitization as the cornerstone for a new approach to pharmacotherapy: drugs as foreign/stressful stimuli. Drug Devel Res 1988; 14:1-30.

23. Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res Rev 1986; 11:157-198.

24. Post RM. Minireview: intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. Life Sci 1980; 26:1275-1282.

25. Kalivas PW, Barnes CD (eds). Sensitization in the Nervous System. Caldwell, NJ: Telford Press, 1988.

26. Post RM, Rubinow DR, Ballenger JC. Conditioning, sensitization, and kindling: implications for the course of affective illness. In Post R, Ballenger J (eds). Neurobiology of Mood Disorders. Baltimore: Williams and Wilkins, 1984, pp. 432-466.

27. Robinson TE, Becker JM, Presty SK. Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: sex differences. Brain Research 1982; 253:231-241.

28. Leith NJ, Kuczenski R. Two dissociable components of behavioral sensitization following repeated amphetamine administration. Psychopharmacology 1982; 76:310-315.

29. Antelman SM, Caggiula AR, Kocan D, Knopf S, Meyer D, Edwards DJ, Barry H. One experience with 'lower' or 'higher' intensity stressors, respectively enhances or diminishes responsiveness to haloperidol weeks later: implications for understanding drug variability. Brain Research 1991; 566:276-283.

30. Kalivas PW, Richardson-Carlson R, Van Orden G. Cross-sensitization between foot shock stress and enkephalin-induced motor activity. Biol Psychiatry 1986; 21:939-950.

31. Antelman SM, Eichler AJ, Black CA, Kocan D. Interchangeability of stress and amphetamine in sensitization. Science 1980; 207:329-331.

32. Cools AR. Differential role of mineralocorticoid and glucocorticoid receptors in the genesis of dexamphetamine-induced sensitization of mesolimbic, alpha 1 adrenergic receptors in the ventral striatum. Neuroscience 1991; 43:419-428.

33. Post RM, Weiss SRB, Pert A. The role of context and conditioning in behavioral sensitization to cocaine. Psychopharm Bull 1987; 23:425-429.

34. Peris J, Decambre N, Coleman-Hardee ML, Simkins JW. Estradiol enhances behavioral sensitization to cocaine and amphetamine-stimulated striatal [3H] dopamine release. Brain Res 1991; 566:255-264.

35. Cabib S, Puglisi-Allegra S. Genotype-dependent effects of chronic stress on apomorphine-induced alterations of striatal and mesolimbic dopamine metabolism. Brain Res 1991; 542:91-96.

36. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992; 149:999-1010.

37. Keller RW, Masonneuve IM, Carlson JN, Glick SD. Within subject sensitization of striatal dopamine release after a single injection of cocaine: an in vivo microdialysis study. Synapse 1992; 11:28-34.

38. Joy RM. Mode of action of lindane, dieldrin, and related insecticides in the central nervous system. Neurobehav Toxicol Teratol 1982; 4:813-823.

39. Gilbert ME. Neurotoxicants and limbic kindling. In Isaacson RL and Jensen KF (eds). The Vulnerable Brain and Environmental Risks. Vol. 1: Malnutrition and Assessment. NY: Plenum Press, 1992.

40. Gilbert ME. Formamidine pesticides enhance susceptibility to kindled seizures in amygdala and hippocampus of the rat. Neurotoxicol Teratol 1988; 10:221-227.

41. Gilbert ME. Proconvulsant activity of endosulfan in amygdala kindling. Neurotoxicol Teratol 1992; 14:143-149.

42. Gilbert ME. A characterization of chemical kindling with the pesticide endosulfan. Neurotoxicol Teratol 1992; 14:151-158.

43. Hooks MS, Jones GH, Neill DB, Justice JB. Individual differences in amphetamine sensitization: dose-dependent effects. Pharmacol Biochem Behav 1992; 41:203-210.

44. Burchfiel JL, Duffy FH. Organophosphate neurotoxicity: chronic effects of sarin on the electroencephalogram of monkey and man. Neurobehav Toxicol Teratol 1982; 4:767-778.

45. Adamec RE. Does kindling model anything clinically relevant? Biol Psychiatry 1990; 27:249-279.

46. Lorig T, Huffman E, DeMartino A, DeMarco J. The effects of low concentration odors on EEG activity and behavior. J Psychophysiology 1991; 5:69-77.

47. Lorig T, Herman KB, Schwartz GE. EEG activity during administration of low-concentration odors. Bull Psychonomic Sci 1990; 28:405-408.

48. Lorig TS. Human EEG and odor response. Prog Neurobiol 1989; 33:387-398.

49. Rosen I, Haeger-Aronsen B, Rehnstrom S, Welinder H. Neurophysiological observations after chronic styrene exposure. Scand J Work Environ Health 1978; 4(suppl):184-194.

50. Ehlers CL, Schuckit MA. EEG fast frequency activity in the sons of alcoholics. Biol Psychiatry 1990; 27:631-641.

51. Mansour A, Doyle R, Katz R, Valenstein ES. Long-lasting changes in behavior and morphine sensitivity following amygdaloid kindling in mice. Physiol Behav 1981; 27:1117-1120.

52. Caldecott-Hazard S. Interictal changes in behavior and cerebral metabolism in the rat: opioid involvement. Exp Neurol 1988; 99:73-83.

53. DaSilva FHL, Gorter JA, Wadman WJ. Kindling of the hippocampus induces spatial memory deficits in the rat. Neurosci Lett 1986; 63:115-120.

54. Alexopoulos GS, Young RC, Shindledecker RD. Brain computed tomography findings in geriatric depression and primary degenerative dementia. Biol Psychiatry 1992; 31:591-599.

55. Alexopoulos GS, Young RC, Lieberman KW, Shamoian CA. Platelet MAO activity in geriatric patients with depression and dementia. Am J Psychiatry 1987; 144:1480-1483.

56. Reding M, Haycox J, Blass J. Depression in patients referred to a dementia clinic. A three-year prospective study. Arch Neurol 1985; 42:894-896.

57. Kral VA, Emery OB. Long-term follow-up of depressive pseudodementia of the aged. Can J Psychiatry 1989; 34:445-446.

58. Girgis M. Biochemical patterns in limbic system circuitry: biochemical-electrophysiological interactions displayed by chemitrode techniques. In Doane BK, Livingston KE (eds). The limbic system: functional organization and clinical disorders. NY: Raven Press, 1986; pp. 55-65.

59. Ghantous H, Dencker L, Gabrielsson J, Danielsson BRG, Bergman K. Accumulation and turnover of metabolites of toluene and xylene in nasal mucosa and olfactory bulb in the mouse. Pharmacol Toxicol 1990; 66:87-92.

60. Dager SR, Holland JP, Cowley DS, Dunner DL. Panic disorder precipitated by exposure to organic solvents in the work place. Am J Psychiatry 1987; 144:1056-1058.

61. Pitman RK, van der Kolk BA, Orr SP, Greenberg MS. Naloxone-reversible analgesic response to combat-related stimuli in posttraumatic stress disorder. A pilot study. Arch Gen Psychiatry 1990; 47:541-544.

62. Orenstein H. Briquet's syndrome in association with depression and panic: a reconceptualization of Briquet's syndrome. Am J Psychiatry 1989; 146:334-338.

63. Orenstein H, Raskind MA, Wyllie D, Raskind WH, Soules MR. Polysymptomatic complaints and Briquet's syndrome in polycystic ovary disease. Am J Psychiatry 1986 143:768-771.

64. Herzog AG, Seibel MM, Schomer D, Vaitukaitis J, Geschwind N. Temporal lobe epilepsy: an extrahypothalamic pathogenesis for polycystic ovarian syndrome? Neurology 1984; 34:1389-1393.

65. Herzog AG, Seibel MM, Schomer DL, Vaitukaitis JL, Geschwind N. Reproductive endocrine disorders in women with partial

seizures of temporal lobe origin. Arch Neurol 1986; 43:341-346.

66. Herzog AG, Russell V, Vaitukaitis JL, Geschwind N. Neuroendocrine dysfunction in temporal lobe epilepsy. Arch Neurol 1982; 39:133-135.

67. Laatikainen T, Salminen K, Virtanen T, Apter D. Plasma B-endorphin, B-lipotropin, and corticotropin in polycystic ovarian disease. Eur J Obstet Gynecol Reprod Biol 1987; 24:327-333.

68. Nappi C, Petraglia F, DiCarlo C, DeRosa R, Zaccardo A, Genazzani AR, Montemagno U. Impairment of dopaminergic and opioidergic activity in patients with polcystic ovarian disease is restored by treatment for the induction of ovulation. Gynecol Obstet Invest 1989; 27:38-41.

69. Aleem FA, Eltabbakh GM, Omar RA, Southren AL. Ovarian follicular fluid B-endorphin levels in normal and polycystic ovaries. Am J Obstet Gynecol 1987; 156:1197-1200.

70. Lobo RA. The role of neurotransmitters and opioids in polycystic ovarian syndrome. Endocrinol Metab Clin N Am 1988; 17:667-683.

71. Williams CL, Peterson JM, Villar RG, Burks TF. Corticotropin-releasing factor directly mediates colonic responses to stress. Am J Physiol 1987; 253:G582-586.

72. Weiss SB, Post RM, Gold PW, Chrousos G, Sullivan TL, Walker D, Pert A. CRF-induced seizures and behavior: interaction with amygdala kindling. Brain Res 1986; 372:345-351.

73. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. J Am Med Assoc 1992; 267:1244-1252.

74. Anselmi B, Baldi E, Casacci F. Endogenous opioids in cerebrospinal fluid and blood in idiopathic headache sufferers. Headache 1980; 21:294-299.

75. Facchinetti F, Martignoni E, Sola D, Petraglia F, Nappi G, Genazzani AR. Transient failure of central opioid tonus and premenstrual symptoms. J Reprod Med 1988; 33:633-638.

76. Chuong CJ, Coulam CB, Kao PC, Bergstralh EJ, Go VLW. Neuropeptide levels in premenstrual syndrome. Fertil Steril 1985; 44:760-765.

77. Casale TB, Bowman S, Kaliner M. Induction of human cutaneous mast cell degranulation by opiates and endogenous opioid peptides: evidence for opiate and nonopiate receptor participation. J Allergy Clin Immunol 1984; 73:775-781.

78. Mediratta PK, Das N, Gupta VS, Sen P. Modulation of humoral immune responses by endogenous opioids. J Allergy Clin Immunol 1988; 81:27-32.

79. Cain DP, Corcoran ME. Epileptiform effects of met-enkephalin, B-endorphin, and morphine: kindling of generalized seizures and potentiation of epileptiform effects by handling. Brain Res 1985; 338:327-336.

80. Snyder-Keller AM. Striatal c-fos induction by drugs and stress in neonatally dopamine-depleted rats given nigral transplants: importance of NMDA activation and relevance to sensitization phenomena. Exp Neurol 1991; 113:155-165.

81. Gilbert ME. The NMDA-receptor antagonist, MK-801, suppresses limbic kindling and kindled seizures. Brain Res 1988; 463:90-99.

82. Morris RGM, Anderson E, Lynch GS, Baudry. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 1986; 319:774-776.

83. Goddard GV, Douglas RM. Does the engram of kindling model the engram of normal long term memory? Le Journal Canadien des Sciences Neurologiques 1975; 385-394.

84. Staudenmayer H, Selner JC. Neuropsychophysiology during relaxation in

generalized, universal 'allergic' reactivity to the environment: a comparison study. J Psychosom Res 1990; 34:259-270.

85. Keller RW, Stricker EM, Zigmond MJ. Environmental stimuli but not homeostatic challenges produce apparent increases in dopaminergic activity in the striatum: an analysis by in vivo voltammetry. Brain Res 1983; 279:159-170.

86. Keller RW, Masonneuve IM, Carlson JN, Glick SD. Within subject sensitization of striatal dopamine release after a single injection of cocaine: an in vivo microdialysis study. Synapse 1992; 11:28-34.

87. Nakashima M, Kajita S, Otsuki S. Reduction of rat striatal thyrotropin-releasing hormone receptors produced by repeated methamphetamine administration. Biol Psychiatry 1989; 25:191-199.

88. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry 1992; 149:443-454

89. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 1992; 42:1328-1335.

90. Steventon GB, Heafield MTE, Waring RH, Williams AC. Xenobiotic metabolism in Parkinson's disease. Neurology 1989; 337:736-739.

91. Calne DB, Langston JW. Aetiology of Parkinson's disease. Lancet 1983; 2:1457-1459.

92. Schwartz GE, Kline JP, Dikman Z, Wright KP, Polak EH. EEG registration of androstenone in androstenone anosmic subjects. Chemical Senses in press.

93. Schwartz GE, Wright KP, Polak EN, Kline JP, Dikman Z. Topographic EEG mapping of conscious and unconscious odors. Chemical Senses in press.

94. Schwartz GE, Wright KP, Polak EH, Schwartz JI. Conscious and unconscious odor registration in the elderly. Chemical Senses in press.

95. Bell IR, Jasnoski ML, Kagan J, King DS. Depression and allergies: survey of a nonclinical population. Psychother Psychosom 1991; 55:24-31.

96. van der Kolk B, Greenberg M, Boyd H, Krystal J. Inescapable shock, neurotransmitters, and addiction to trauma: toward a psychobiology of post traumatic stress. Biol Psychiatry 1985; 20:314-325.

97. Becker A, Grecksch G, Matthies H. Influence of beta-casomorphin derivatives on chemically and electrically induced seizures. Peptides 1991; 12:43-45.

98. Blass EM, Fitzgerald E. Milk-induced analgesia and comforting in 10-day-old rats: opioid mediation. Pharmacol Biochem Behav 1988; 29:9-13.

99. Blass EM, Shide DJ, Weller A. Stress-reducing effects of ingesting milk, sugars, and fats. A developmental perspective. Annals NY Acad Sci 1989; 575:292-306.

100. Blass EM, Hoffmeyer LB. Sucrose as an analgesic for newborn infants. Pediatrics 1991; 87:215-218.

101. Bell IR, Schwartz GE, Meredith KE, Ritenbaugh C, Graver E. Fat and sweet food intake by older adults: relationship to distress and personality traits. Submitted for publication.

102. Parker SL, Leznoff A, Sussman GL, Tarlo SM, Krondl M. Characteristics of patients with food-related complaints. J Allergy Clin Immunol 1990; 86:503-511.

103. Markley EJ, Margen S, King DS, Bell IR, Lazarus RS. Daily hassles, mastery, and psychological symptoms: are they related to perceived adverse reactions to food? Submitted for publication 1992.

104. Egger, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double-blind controlled trial of oligoantigenic

diet treatment. Lancet 1983; 2:865-869.

105. Egger J, Carter CM, Soothill JF, Wilson J. Oligoantigenic diet treatment of children with epilepsy and migraine. J Pediatrics 1989; 114:51-58.

106. Caggiula AR, Antelman SM, Aul E, Knopf S, Edwards DJ. Prior stress attentuates the analgesic response but sensitizes the corticosterone and cortical dopamine responses to stress 10 days later. Psychopharmacology 1989; 99:233-237.

107. Kilburn KH. Is the human nervous system most sensitive to environmental toxins? Arch Environ Health 1989; 44:343-344.

108. Kilburn KH, Warsaw RH, Shields MG. Neurobehavioral dysfunction in firemen exposed to polychlorinated biphenyls (PCBs): possible improvement after detoxification. Arch Environ Health 1989; 44:345-350.

109. Bokina AI, Eksler ND, Semenenko AD, Merkuryeva RV. Investigation of the mechanism of action of atmospheric pollutants on the central nervous system and comparative evaluation of methods of study. Environ Health Perspect 1976; 13:37-42.

110. Henriksen HJ, Bloom FE, McCoy F, Ling N, Guillemin R. Beta-endorphin induces nonconvulsive limbic seizures. Proc Natl Acad Sci 1978; 75:5221-5225.

111. Randolph TG. Specific adaptation. Annals Allergy 1978; 40:333-345.

112. Cummings JL, Benson DF. Dementia. A clinical approach. 2nd ed. Boston: Butterworth-Heinemann, 1992.

113. Bell IR, Schwartz GE, Miller CS. A time-dependent sensitization approach to nonatopic multiple chemical, drug, and food sensitivities: opioids as prototypical stimuli. Submitted for publication.

TABLE 1

TIME-DEPENDENT SENSITIZATION

pharmacological & nonpharmacological stimuli cross-react
foreignness, novelty, stressfulness of stimuli mobilize
intermittent exposure schedule favors
hyperreactivity to novelty predicts
low doses, not high doses, elicit sensitizability

opioids activate
estradiol accelerates, testosterone lessens
glucocorticoids accelerate

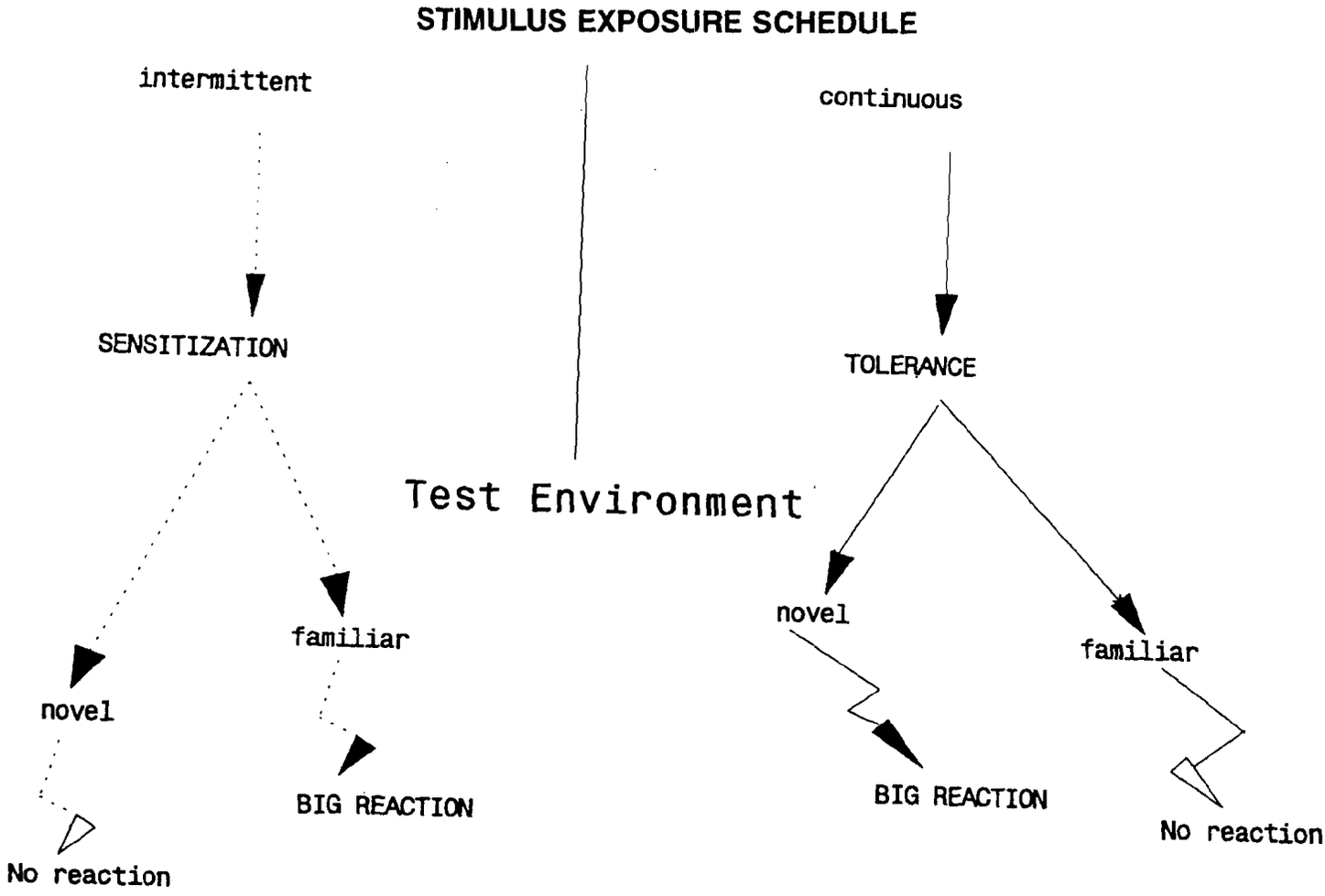
excitatory amino acids mediate
learning & memory pathways participate

TABLE 2

APPROACHES TO DIFFERENTIATING MCS FROM AFFECTIVE DISORDERS

1. responses to low level chemical exposures tested in intermittent, *multiple repeated* sessions under the same conditions
2. neuropsychological/cognitive test performance patterns
3. balance and gait disturbances in MCS
4. PET and SPECT brain scan differences
5. quantitative EEG pattern differences

FIGURE 1


STIMULUS EXPOSURE SCHEDULE
intermittent
continuous
SENSITIZATION
TOLERANCE
Test Environment
novel
familiar
novel
familiar
BIG REACTION
BIG REACTION
No reaction
No reaction

THE ENVIRONMENTAL CONTROL UNIT (ECU) IN THE DIAGNOSIS OF CHEMICAL SENSITIVITY

and

RECENT FINDINGS OF NEUROTOXIC ABNORMALITIES ON BRAIN SPECT IMAGING OF PATIENTS WITH CHEMICAL SENSITIVITY

Gerald H. Ross, M.D., C.C.F.P.,
D.I.B.E.M., F.A.A.E.M.

Presented at

"Multiple Chemical Sensitivities and Their Relevance to Psychiatric Disorders"

HEALTH AND WELFARE CANADA CONFERENCE

Chateau Laurier - Ottawa, Canada

December 7, 1992

PART I: THE ENVIRONMENTAL CONTROL UNIT (ECU) IN THE DIAGNOSIS OF CHEMICAL SENSITIVITY.

ABSTRACT

An environmental control unit (ECU) is a specialized, in-hospital facility constructed in a manner to bring about significant reductions in the contaminants in the controlled indoor atmosphere. It utilizes materials and furnishings that have low outgassing or offgassing, and which therefore have a minimum potential for contamination of the indoor environment. In such a facility patients consume organically grown, chemically less contaminated produce and drink pure bottled water from glass containers. The unit air is highly filtered to reduce both particulates and common indoor chemical pollutants, like volatile organic compounds (VOC's). Inside an ECU, patients with either classical allergy and/or chemical sensitivity can be stabilized, monitored and tested with a minimum of extraneous complicating factors that might trigger symptoms and interfere with the validity of testing results. In an ECU, patients become isolated from and thus deadapted to environmental factors which may be potential triggers of adverse symptoms and ill health. Both allergic and chemically sensitive patients usually improve dramatically in the ECU. After deadaptation, diagnostic controlled challenges can be undertaken either orally, intradermally, or by double blind placebo-controlled inhalant exposures. Because of the nature of its construction and operation, the Environmental Control unit is an ideal facility for both the diagnosis and treatment of chemical sensitivity.

Thomas A. Edison is widely quoted as having said "The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, in diet, and in the cause and prevention of disease." It is unlikely that even Edison with his genius could have foreseen the widespread changes that have come upon modern society, in which we are instructed: "Don't breathe the air. Don't drink the water. Don't eat fruit, vegetable, meat, fish, sugar, salt, or fats. Don't have sex ever again..... But have a nice day."

Edison was undoubtedly speaking of the complex interaction between human beings and their total environment, the latter of which includes the foods, chemicals, microbes and inhalants to which we are exposed, and even our genetic endowment, nutritional status, the level of emotional stress and electromagnetic fields. Our "health" or lack thereof is an expression of the complex interaction of these factors.

The cover of "Chemical and Engineering News" of July 22, 1991, shows an outlined figure of Rodin's Thinker, pondering on the topic Multiple Chemical Sensitivity, which was the focus of that issue. I would highly recommend the review article on MCS contained in this journal.

The question this conference addresses is the relationship between multiple chemical sensitivities and psychiatric illness. I would submit to you that these conditions are not the same, although like many chronic illnesses, there may be some overlap. Based on five years of clinical experience, I would estimate that less than 2-3% of patients who have chemical sensitivity exhibit any significant psychiatric disease other than reactive depression, which might be expected under the circumstances.

The first part of my presentation today, however, is "The Environmental Control Unit in the Diagnosis of Chemical Sensitivity". To understand the helpful nature of the Environmental treatment and diagnosis of chemical sensitivities, it is essential that we grasp the concept of the "total load." The total load is the cumulative effect of all those stressors that the person must adapt to, detoxify or cope with in some manner (Randolph, 1965). The total load includes such factors as foods, chemicals, inhalants, microbes, physical phenomena, genetic factors, nutritional deficits, electromagnetic forces, emotional stress and others.

An Environmental Control Unit (Sprague, 1987) is built using the same principles as shown exhibited at The Environmental Health Center - Dallas, which has significant restrictions on the potential contaminants which are permitted to come inside the controlled atmosphere of the facility. (For example, there are no newspapers, pesticides, food or drink, perfumes, aftershaves, hair spray and other

scented or aromatic substances.) The walls and ceiling are made of porcelain-on-steel, and have the appearance of the surface of a bathtub. The floors are all Terrazzo tile laid with a non-toxic grout. The air is highly filtered through both particulate and charcoal filters to remove volatile organic chemical contaminants in the air.

Even the computer systems used in the controlled atmosphere are contained within stainless steel boxes, the air from which is evacuated through charcoal filters to savage those chemical substances which will come off the warm plastic and printed circuits.

Inside such a facility, patients who have either classical allergy and/or chemical sensitivity can be tested and evaluated with a minimum of extraneous complicating factors that might interfere with the validity of testing results. Many patients report feeling very substantially better within 30 minutes of entering this kind of filtered atmosphere.

The Occupational and Environmental Unit at Tri City Hospital in Dallas is built using similar principles. Some of the rooms have tiled walls, others have porcelain-on steel, and others have plaster, to provide a variety of environments to meet individual patient's needs. The mattresses are all hand made using blankets only. The furniture is either stainless steel or solid wood. In addition to the central air handling mechanisms, each room has its own individual air filtration and air conditioning device.

An Environmental Control Unit or similar facility is constructed with an awareness of the principle of "outgassing" or "offgassing". All substances are in a state of dynamic change, and the amount of outgassing from very solid material is substantially less than from softer materials. Stone is generally one of the least reactive, followed by ceramic, steel, iron, hardwood, and so on. Within the petroleum based products, the most outgassing is seen in polyesters, followed by polyethylene, polyvinyl, and silicones.

This is one explanation why many chemically sensitive patients become quite unwell when they wear polyester clothing. Even though we may not be able to smell any substances coming out of this kind of fabric, it is well known that the polyester fabrics will outgas and release chemical substances that have gone into their manufacture.

Inside an Environmental Control Unit, patients drink only pure water such as distilled or spring water bottled in glass, and consume organically grown, chemically less contaminated foods.

The Environmental Control Unit is an excellent facility for evaluation or confirmation of chemical sensitivity (Rea, 1989). This determination is usually made using two sources of information, those being the history and physical examination, followed by specific testing. The latter is usually done intradermally or by inhalation, or by oral food challenge.

When it comes to challenge testing, of whatever type, it is important to remember another principle that is frequently seen in these patients, which is bipolarity of response (Randolph, 1980). This is a biphasic response to some trigger, comprised of two distinct components that usually involves a stimulation phase followed by a withdrawal or depressive phase. A classic example of this is the effect of alcohol, but this bipolar effect may be seen in response to foods, inhalants, chemicals or other factors. This bipolarity of response to environmental incitants is frequently overlooked in medicine in general.

At any one time, we are being influenced by a variety of environmental triggers in the form of foods and chemicals that may have induced a spectrum of stimulatory or withdrawal affects upon us. Many times these biphasic responses cancel out or completely cloud the issue as to whether a specific trigger was responsible for the induction of certain symptoms.

Within the Environmental Control Unit, however there is a minimum of extraneous factors to induce potential adverse effects in these patients. The patient has usually fasted for several days, consuming plenty of pure water. During this phase there may be an exacerbation of symptoms, because of the withdrawal phase of the biphasic response, which is also called deadaptation. In the Environmental Control Unit, the patient is usually started on a rotational dietary pattern, to give a nutritionally adequate variety of foods, while minimizing exposures to foods to which the patient

may be sensitive.

After the patient has become deadapted, however, individual challenge studies can be performed, with a much better likelihood of a demonstrable cause and effect relationship being seen between the stimulus and some adverse response, should the patient be sensitive to that substance. Intradermal testing can be done in a variety of ways but we usually use serial dilution endpoint titration (AMA, 1987) and/or provocation neutralization (King, 1988a, King 1988b). If performed by experienced testers under environmentally controlled circumstances, these techniques can give very reliable data, especially when done on a blinded basis.

The second main investigative technique used to determine chemical sensitivity is that of the double blind placebo controlled, inhaled challenge (Rea, 1989). This can be done in the Environmental Control Unit or other similar facility, in an enclosed glass and anodized aluminum booth. Inside such a booth the patient can be exposed to specific concentrations of chemical substances, at concentrations that are below the odor threshold along with placebos. If these are done under environmentally controlled circumstances, very specific and reproducible results can be obtained. This technique uses not only the subjective response of the patient, but gathers parametric data from vital signs, neurocognitive testing and other hard data such as autonomic neurological function, to determine what relationship, if any, there is between the chemical exposure and the patient's symptoms and/or signs.

However, there are specific criteria which are essential for reliable testing with this technique: (a) it must be performed under environmentally controlled circumstances; (b) before testing, the patient must be deadapted to foods and pollutants; (c) the patient must be on relatively safe food and water before testing is started; (d) the testing booth must be non polluted; (e) signs and symptoms appropriate to the problem must be measured; and (f) each inhaled challenge must be performed using the type of chemical, the dose and the time of exposure that is appropriate under the circumstances.

One of the specific techniques that we make use of at the Environmental Health Center - Dallas is that of evaluation of the autonomic neurological function by binocular Iriscorder and pupillography (Shirakawa, 1992). The pupillary response to light stimulus is specifically measured by a computerized scanning device developed by Hamamatsu Photonics of Japan.

Using such hard parametric data, specific physiological changes can be detected on chemical or other challenge, even at dosages far below the odor threshold, and can demonstrate significant deviations from base line, when chemically sensitive patients are exposed to a substance to which they are reactive. Especially when done in a double blind, placebo controlled manner, this particular type of testing technique can give very firm evidence for the ruling in or out of chemical sensitivity to that substance being tested.

In summary, because of its very nature, the ECU is an ideal facility for both the diagnosis and treatment of chemical sensitivity, as long as such programs are conducted by professionals who understand and use the principles outlined above. The controlled atmosphere of the ECU provides an ideal facility for specific scientific research to enlarge our understanding of the nature of chemical sensitivity and how we can best help these unfortunate patients.

REFERENCES

AMA Council on Scientific Affairs. (1987). In Vivo Diagnostic Testing and Immunotherapy for Allergy. Report 1, Part 1. JAMA 258 (10): 1363 - 1367.

SPRAGUE, D. (1987). The concept of an environmental control unit. In: Food Allergy and Intolerance. (J. Brostoff and S. Challacombe, eds.). Bailliere Tindall, London. pp. 947-960.

RANDOLPH, T., MOSS, R. (1980). An Alternative Approach to Allergies. Lippincott and Crowell, New York.

REA, W.J., ROSS, G.H., JOHNSON, A.R., et al. (1989). Confirmation of chemical sensitivity by means of double-blind inhalant challenge of toxic volatile chemicals. Clinical Ecology 4(3): 113-118.

RANDOLPH, T. (1965) The ecologic orientation in ıedicine: comprehensive environmental control in diagnoses and therapy. Ann. Allergy 23: 7-22.

SHIRAKAWA, S., REA, W.J., ISHKAWA, S., JOHNSON, A.R. (1992). Evaluation of the autonomic nervous system response by pupillographical study in the chemically sensitive patient. Environmental Medicine. 8(4): 121-127.

KING, W.P., FADAL, R.G., WARD, W.A., et al. (1988a). Provocation - Neutrilization: A two-part study. Part I: The intracutaneous provocative pool test: A multi-center comparison study. Otolaryngology - Head and Neck Surgery. 99(3): 263-271.

KING, W.P., FADAL, R.G., WARD, W.A., et al. (1988b). Provocation - Neutralization: A two-part study. Part II: Subcutaneous neutralization therapy: a multi-center study. Otolaryngology - Head and Neck Surgery. 99(3): 272-277.

PART II: RECENT FINDINGS OF NEUROTOXIC ABNORMALITIES ON BRAIN SPECT IMAGING OF PATIENTS WITH CHEMICAL SENSITIVITY

ABSTRACT

MCS patients frequently report problems with memory, concentration, emotional swings, irritability, and poor mental organizational skills, vhich is sometimes given the global description of 'brain fog." Frequently these symptoms may have physiological triggers but be mistaken for psychiatric symptomatology. An exciting recent advance in the investigation of the chemically sensitive patient involves brain SPECT scanning (Single Photon Emission Computer Tomography) which is a metabolic or functional scan of brain activity. Many patients with symptoms of chemical sensitivity who report significant neurocognitive deficits are being found to have a specific pattern of diffuse cortical filling defects on SPECT imaging, which is distinctly different from those abnormalities associated with psychiatric problems. The diffuse intracerebral defects closely resemble the pattern previously identified from neurotoxic injury. Eighty-eight percent of chemically sensitive patients (35 of 40 patients, compared to none of ten normal control subjects) with neurocognitive complaints were found to have abnormal SPECT scans with diffuse cortical filling defects. Further studies are proceeding using this investigative technique, which permits an assessment of a possible physiological basis for the multiple neurological and neurocognitive signs and symptoms reported by patients with chemical sensitivity.

For many years MCS patients have reported problems with memory, concentration, emotional swings with irritability and poor mental organizational skills. Often this is termed under the global description of "brain fog", in which the patient knows that they are impaired in comparison to their normal cerebral functioning. This cluster of symptoms may well have physiological triggers, but may be mistaken for psychiatric symptomatology.

If such symptoms were truly generated on exposure to chemical substances to which the patient was sensitive, it would not be surprising if widespread metabolic defects were taking place in the patient's brain, as a consequence of a perceived or unperceived exposure.

A recent exciting advance in the investigation of the Chemically Sensitive patient centers around brain imaging with SPECT (single photon emission computed tomography). Unlike CT or MRI scan, SPECT imaging is a metabolic or functional scan that reflects the biochemical activity of the intracranial structures, using a tracer which has been tagged with radioactive technetium-99 (reference).

Dr. Thomas Callendar has previously reported on abnormalities on the SPECT imaging in chemically sensitive patients (Callendar, 1991). At the